In the United States District Court Eastern District of Washington

City of Spokane v. Monsanto Co.

Expert Rebuttal Report of

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1. REBUTTAL COMMENTS: DRS. KEENAN AND EATON

This rebuttal report focuses primarily on the opinions expressed in the expert reports of Drs. Keenan and Eaton.[1] Both have expressed opinions on whether the Spokane polychlorinated biphenyl (PCB)-contaminated fish pose a threat to the public based on human health risk assessments. My rebuttal responses address both the risk assessment methodology they used to support their conclusions that PCBs do not pose either a noncancer health hazard or cancer risk, as well as their conclusions.

1.1. Rebuttal Responses to Dr. Keenan's Opinion

1.2. Dr. Keenan Does Not Use the U.S. EPA or DOH Standard Protocol for Evaluating Fish Risk

My general rebuttal opinion for Dr. Keenan's analysis of PCB-related health is that he relies on a risk assessment approach that is neither appropriate nor necessary to specifically address the public health threat posed by PCBs.

I have conducted approximately 100 Human Risk Assessments for PCB-contaminated sites and have also assisted or been technically involved with seven state departments of health (and the Agency for Toxic Substances and Disease Registry [ATSDR]) to assist them in choosing the best toxicological approach and methods that would yield the best and most-detailed results. In these efforts, I have always recommended following the most scientifically tenable approach that introduces the least amount of uncertainty and would provide credible results.

As I discussed in Volume 3 of my expert report, while the U.S. Environmental Protection Agency (EPA) is the environmental regulatory agency charged with enforcing remediation according to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); and other

[1] I also addresses certain points made by Dr. Desvousges and Mr. Herman, as noted throughout.

statutes, it does not typically oversee or engage directly in matters relating to developing fish advisories specifically for protecting the public with detailed recommendations for fish consumption. Those types of analyses are typically performed by ATSDR (which is the only Agency that is specifically charged by Congress to protect public health). If requested by states, ATSDR collaborates with the state health department to conduct a Health Consultation in which the health threats posed by eating contaminated fish are evaluated and a fish consumption advisory is formulated.

The distinctions between the types of health studies performed by U.S. EPA as opposed to those conducted by ATSDR and state health departments are very important. The scientific methodologies used by the two groups are very different because the goals are different, and the results and conclusions are used for different purposes. Dr. Keenan's opinion relies on the probabilistic U.S. EPA Human Health Risk Assessment (HHRA) methodology he used to conclude that PCB-contaminated fish do not pose a significant health threat to Spokane fish consumers. While I will provide some critiques of the specific assumption his HHRA is based on, my rebuttal opinion is that he simply used the wrong scientific approach. While the issues in this case focus on the health threats from eating contaminated fish, his approach is best suited to a U.S. EPA-type investigation in which there is only one issue that needs to be addressed: does the contaminated site pose unacceptable risk or not? Answering this single question is the sole goal of an HHRA for a U.S. EPA site where the goal is to decide whether remediation needs to be enforced or not. The Spokane River is not a U.S. Superfund site; therefore, an HHRA is an inappropriate methodology to apply in this case. Essentially Dr. Keenan has come to *one* conclusion: the fish tissue levels of PCBs do not pose a significant human health risk (i.e., the risks are acceptable). I have already discussed the issue of what is an acceptable risk level in Volume 3 of my report. The standard Dr. Keenan relies on is, once again, a U.S. EPA standard that was developed specifically to determine whether or not U.S. EPA has reasonable scientific justification for enforcing remediation. What he fails to acknowledge is that an HHRA is used to support a U.S. EPA decision, and the acceptable risk level framework he is basing his conclusions on is not appropriate for this case. U.S. EPA's acceptable risk framework is based on many factors, including cost and the practicality of remediation.. The acceptable risk framework is not relevant to this case. Dr. Keenan's HHRA conclusions stand in stark contrast to those of Washington State Department of Health (DOH) experts, triggering the hypothetical question: *"If Dr. Keenan is correct and PCB-contaminated fish tissue really do not pose an unacceptable risk, then the DOH Fish Consumption Advisories are not justified and should be considered unnecessary and stopped."* In other words, both DOH and Dr. Keenan cannot be correct regarding the threat posed by eating PCB-contaminated fish; one must be incorrect.

My opinion is that Dr. Keenan has used an inappropriate methodology to evaluate the health threat posed by eating PCB-contaminated fish and that the protocols developed over the last decade and implemented by DOH constitute the appropriate method for evaluating health threats and making public health recommendations to protect the public, as DOH is charged to do. While the U.S. EPA HHRA methodology Dr. Keenan has used to support his opinion is a generally accepted approach for U.S. EPA sites, where only one single calculated risk estimate is needed to justify determination of whether or not to remediate, river cleanup to remove PCBs from the sediments is not an issue here.

Dr. Keenan's conclusions appear to primarily pertain to the average sport fisherman. He ignores the possibility that the fish consumption surveys could be biased because he does not take into account fish consumers who may be ignored. This would include those who live in poverty or may not want to "get involved" with regulatory authorities. Nevertheless, Dr. Keenan accepts the survey information as fact.

DOH is the lead state agency charged with protecting the entire Spokane fish consumer population. DOH is following and providing detailed information to the public about what types of fish are safe to eat and in what quantities (i.e., per month).

In applying his HHRA methodology to determine whether PCB-contaminated fish pose an unacceptable risk, Dr. Keenan relied on a mathematical "simulation" with numerous hypothetical populations and assumptions about PCB exposures. While he supports these hypothetical assumptions with studies, it is important to know the strengths and weaknesses of the studies themselves because of how he defines the hypothetical assumptions and what population he is representing in his HHRA. For example, while Dr. Keenan makes assumptions about the fish ingestion rate, it is important to define the population that his ingestion rate represents. Indeed, defining the ingestion rate is perhaps the single-most important assumption in any HHRA. In my experience as an U.S. EPA consultant and expert witness, the fish consumption ingestion rate is the most important assumption in an HHRA because it is the focus of heated disagreement and arguments both in court and in negotiating a remedy for U.S. EPA lead remedial investigations. What is lost in many of these disagreements is that the "true" fish consumption rate can never be verified because there is a great deal of uncertainty in data gathered in fish consumption surveys, which is widely recognized in the field of toxicology. DOH has conducted numerous fish consumption surveys and has candidly admitted to and pointed out areas of uncertainty (which I discuss below). The importance of this single fish consumption assumption cannot be overstated as it is literally the key assumption that—for many contaminated rivers—governs whether the risks calculated in an HHRA are acceptable or unacceptable. I have never encountered a state health department that has used the type of

probabilistic HHRA Dr. Keenan used to evaluate the health risks from fish ingestion for the purpose of protecting the public. Nor to my knowledge has it been used to develop fish consumption advisories.

To avoid the numerous hypothetical assumptions necessary when conducting a complex HHRA, most state health departments follow a much more simplified and scientifically tenable risk assessment approach. This is the approach that all states, including Washington State DOH, follow because it is far superior and more direct in evaluating whether specific species from different rivers are safe to eat and, if not, how many fish can be eaten without toxic effects being manifest. The reason the DOH risk evaluation is so superior is that it does not rely on hypothetical simulations, fish consumption rates, or other assumptions that cannot be verified.

The scientific methodology used by DOH to develop fish advisories for PCB-contaminated fish is simply based the "safe" daily intake of PCBs; it is unnecessary to calculate the site-specific fish consumption rates because they do not need to be considered. In fact, the DOH scientific approach is elegant in its simplicity, and the only data needed to evaluate the health threat posed by PCBs is the safe dose, or reference dose (RfD), and the fish tissue PCB concentrations. With this approach, there is no need to dispute the assumed site-specific fish consumption rates nor any other hypothetical scenario. I explain this scientific method in detail in Section 1.3 and provide a simple analogy.

Finally, it should be noted that even U.S. EPA uses the same equations and methodology as DOH when it evaluates the risk from eating contaminated fish (this is general guidance). In fact, U.S. EPA developed the fish risk assessment methodology DOH uses, as stated by the Washington Department of Ecology (DOE): [1]

> *DOH uses an approach similar to that in EPA's Guidance for Assessing Chemical Contaminant Data for use in Fish Advisories Vol. 1-4 for assessing mercury, PCBs, and other contaminants (EPA, 2000). These guidance documents provide a framework from which states can evaluate fish tissue data to develop fish consumption advisories, based on sound science and established procedures in risk assessment, risk management, and risk communication.* [1]

The referenced document is one I have relied on for many years for fish risk assessments because it was specifically developed for state health departments whose mandate is to protect the general public of their states. U.S. EPA's Executive Summary states the overarching goal of its fish risk assessment guidance, which is to provide "state, local, tribal, and federal agencies*"* with a "standardized" risk assessment methodology for fish ingestion: [2]

> *State, local, tribal, and federal agencies currently use various methods to estimate*

> *risks to human health from the consumption of chemically contaminated, noncommercially caught fish and shellfish. A 1988 survey, funded by the U.S. Environmental Protection Agency (EPA) and conducted by the American Fisheries Society, identified the need for standardizing the approaches to evaluating risks and developing fish consumption advisories that are comparable across different* jurisdictions. *Four key components were identified as critical to the development of a consistent risk-based approach: standardized practices for sampling and analyzing fish, standardized risk assessment methods, standardized procedures for making risk management decisions, and standardized approaches to risk communication.*
>
> *To address concerns raised by the survey respondents, EPA has developed a series of four documents designed to provide guidance to state, local, tribal, and regional environmental health officials responsible for issuing fish consumption advisories.* [2]

Dr. Keenan's HHRA is not a standard approach, nor am I aware of any state health department that uses a probabilistic HHRA to protect the public for any type of health evaluation including fish consumption advisories.

That is, the underlying basis for fish consumption advisories is to issue alerts and warnings about contaminated fish and that is *solely* based on the RfD, which requires no information about fish consumption rates. For example, to alert the public about eating contaminated fish U.S. EPA often issues alerts about the health risks as a public service and not to support remediation. For example, it has prepared a detailed risk analysis for fish contaminated with mercury (Hg), which is a nationwide contamination problem because Hg is an airborne contaminant that does not recognize state boundaries. Thus, it is important for every state health department to know how to conduct risk assessments and fish consumption advisories to protect the general public from the toxic effects from this ubiquitous contaminant.

To address the risks posed by eating fish contaminated with Hg, the U.S. EPA and the U.S. Food and Drug Administration (FDA) developed a detailed website, complete with numerous risk assessment guidance documents. [3] (See Exhibit 1.)

Exhibit 1. U.S. EPA Risk Assessment for Fish Contaminated with Mercury [3]

EPA-FDA Fish Advice: Technical Information

This webpage contains detailed information on the underlying calculations for the fish advice for women of childbearing age (about 16-49 years old), pregnant and breastfeeding women, and parents and caregivers of young children. It contains the following information:

1. How the chart for FDA's and EPA's fish advice was derived.
2. Sortable table of fish species that contains data used in separating the fish into categories, such as mercury concentrations and the number of weekly servings.
3. Recommended portion sizes for children based on age.

The approach U.S. EPA and the FDA used to evaluate risks from eating Hg-contaminated fish was solely based on the RfD. As I stated above, it is not necessary to develop a fish ingestion rate with this approach, as the risk is based only on the safe daily intake as described in Exhibit 2.

Exhibit 2. U.S. EPA–FDA Relies Solely on the RfD for Fish Risk Assessments [3]

How FDA and EPA derived the categories in the fish chart

The agencies decided which category each fish belonged to by calculating the highest average amount of mercury that could be in a fish when eaten one, two, and three times a week without going over the maximum acceptable mercury intake amount for an average pregnant woman. The agencies determined the maximum acceptable intake amount by comparing the reference dose (RfD) developed by EPA to the predicted exposure from the consumption of different fish species. An RfD is determined to be a rate of exposure that a person can experience over a lifetime without appreciable risk of harm; however, the RfD for mercury is protective of neurodevelopmental effects from a critical window of development for a fetus during pregnancy. The RfD includes a 10-fold uncertainty factor to allow for variability among individuals and groups, including individuals who are not pregnant. By expressing the advice in terms of recommendations for weekly intake of fish based on the RfD, the agencies aim to help consumers reduce exposure to mercury, while also enabling them to achieve the health benefits from eating fish. We describe the equations and results for determining which fish we placed in each category below.

Exhibit 3 shows that the U.S. EPA–FDA scientific approach uses an equation similar to that used by DOH and that is solely based on the RfD. More importantly, it does not address the issue of a site-specific fish ingestion rate.

Exhibit 3. U.S. EPA–FDA Equations For Fish Risk Assessments [3]

Equations for determining which category each fish went in

The boundaries for each category (or screening values) were calculated using equation 5-4 from EPA's *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis Third Edition*

$$SV = \frac{RfD * BW}{CR}$$

where
SV = screening value for a noncarcinogen (µg/g)
RfD = reference dose (µg mercury/kg-d)
BW = body weight (kg)
CR = mean daily consumption rate of the species of interest (g/d)

For this fish advice, we used the screening value as the highest average amount of mercury in fish that would not exceed the reference dose at a given consumption rate. The consumption rate (CR) was calculated using the following equation:

$$Daily\ consumption\ rate\ \left(\frac{g}{d}\right) = serving\ size\ \left(\frac{oz}{serving}\right) * \frac{28.3\ g}{oz} * weekly\ servings\ \left(\frac{servings}{wk}\right) * \frac{1\ wk}{7\ d}$$

It should be stressed that while a "fish ingestion rate" is one of the parameters listed in the EPA–FDA equation, this term is not the same as the *site-specific* fish ingestion rate Dr. Keenan used in his probabilistic risk assessment. Rather, the above refers to the minimum recommended fish consumption rate to promote a healthy diet that is recommended by U.S. EPA–FDA—8 to 12 ounces per week. That is, the fish ingestion rate is a dietary recommendation used to determine the number of fish meals that will protect pregnant women or women of childbearing age. [3]

1.3. DOH Fish Consumption Advisories

The current (2019) DOH Fish Consumption advisory is presented in Exhibit 4. This table shows that the number of recommended fish meals per month is species and location specific. DOH considers these meal rates to be protective; exceeding them could produce toxicity.

Exhibit 4. Current, 2019 DOH Fish Consumption Advisories [4]

Fish Species	Advisory	Contaminant	Location Description
Spokane Arm - Mouth upriver to Little Falls Dam			
Largescale Sucker	Up to 1 meal per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Brown Trout	Up to 4 meals per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Rainbow Trout	Up to 4 meals per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Little Falls Pool - Little Falls Dam to Long Lake Dam			
Largescale Sucker	Up to 4 meals per month	PCBs, PBDEs, Mercury	Little Falls Pool - Little Falls Dam to Long Lake Dam
Northern Pikeminnow	Up to 4 meals per month	PCBs, PBDEs, Mercury	Little Falls Pool - Little Falls Dam to Long Lake Dam
Long Lake (Lake Spokane)			
Largescale Sucker	Up to 1 meal per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Mountain Whitefish	Up to 2 meals per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Northern Pikeminnow	Up to 2 meals per month	-	Long Lake (Lake Spokane)
Rainbow Trout	Up to 4 meals per month	-	Long Lake (Lake Spokane)
Brown Trout	Up to 1 meal per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Common Carp	Do not eat	PCBs	Long Lake (Lake Spokane)
Yellow Perch	Up to 8 meals per month (healthy choice)	-	Long Lake (Lake Spokane)
UpRiver Dam to Nine Mile Dam			
Largescale Sucker	Up to 2 meals per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Mountain Whitefish	Up to 1 meal per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Rainbow trout	Up to 2 meals per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Idaho Border to Upriver Dam			
All Fish (Spokane River)	Catch and release only	PCBs, PBDEs, Lead	Idaho Border to Upriver Dam

I have conducted more than 100 HHRAs (and teach a Human Health Risk Assessment graduate-level course). I have also assisted many state health departments in developing fish consumption advisories (which have been based on the U.S. EPA fish risk assessment methodology [2] that DOH also follows). I have extensive knowledge of the two types of investigations and lecture on the strengths and weaknesses of these two types of health studies. My opinion is that the U.S. EPA/DOH methods are the best means with which to determine the level of fish that can be consumed safely.

While an HHRA is typically conducted for hazardous waste sites where U.S. EPA is the lead governmental agency, an HHRA does not provide any information on how much contaminated fish can be eaten by fish consumers in the general population or the risk from eating specific fish. It is very limited because it provides only a single combined risk assessment to simulate the "best estimate" risk for the assumed population. U.S. EPA typically conducts an HHRA to determine if remedial action should be taken to clean up hazardous contaminants in a river, and Dr. Keenan's HHRA would be appropriate for that type of analysis. But his HHRA cannot be used to protect, inform, and warn the public about the health threat from specific species at different areas. As I discussed in Volume 3 of my report, ATSDR and State health agencies are responsible for protecting the public. U.S. EPA is responsible for enforcing cleanup. In other words, the sole purpose of an U.S. EPA HHRA is to determine if remediation is necessary and to provide technical support for any decisions made—particularly if those decisions or efforts are challenged in court. Simply put, an HHRA provides no health information to the public

regarding the safe level of fish consumption. In fact, I have extensive experience in my toxicology practice in which the HHRA results indicated there is no health threat, but a fish consumption analysis was necessary to prevent toxic effects. In this case, DOH's finding that fish consumption advisories are necessary to protect the public contradicts Dr. Keenan's conclusion that eating PCB-contaminated fish does not pose a health risk. In other words, there would never be a need for a fish advisory in cases where an HHRA concluded that eating contaminated fish did not pose a health risk The fact that DOH has developed fish advisories supports my opinion that Dr. Keenan's HHRA is either wrong or is misleading, since both Dr. Keenan and DOH cannot both be correct. Dr. Keenan's conclusions seem to indicate Spokane fish consumers need no protection and that the fish consumption advisories are a waste of effort and time.

In contrast to Dr. Keenan's HHRA, the DOH Fish Consumption Advisories provide reasonable, actionable, and useful information that members of the public can use to protect their health. These are the fundamental reasons that health agencies rely solely on the safe daily exposure levels represented by the RfD rather than HHRAs (which are unnecessary). Put another way, if HHRAs provided verifiable health information, health agencies would be conducting them; after all, they have experts who routinely conduct both types of health evaluations. Those experts have concluded that—from a toxicological perspective—fish consumption advisories are the most scientifically tenable investigations. HHRAs are limited in that the risks described in HHRAs can never be verified as the "true" risks (e.g., the calculated risks can never be proven or substantiated by actual cancer incident rates). The mathematical models are built on numerous hypothetical scenarios. The following sections briefly highlight these two types of health assessments and provide some contrasting features. These points support my opinion that, in this case, the DOH Fish Consumption Advisories should be given deference, as they rely entirely on the RfD, or daily safe dose.

1. Fish Consumption Advisory: This type of health evaluation calculates the maximum number of PCB-contaminated fish that can be safely eaten before toxic effects could become manifest. That is, when fish consumers do not exceed the maximum number of fish meals presented in the DOH Fish Consumption Advisory, no PCB-related toxicity should occur. This type of toxicological analysis relies *only* on the "safe" daily intake of PCBs that has been well-established. The safe daily intake is represented by the single toxicity value-the RfD. Simply put, by relying only on the safe daily intake, the fish consumption advisories are not confounded by hypothetical assumptions. Most importantly, they do not rely on fish consumption surveys, which may be biased (due to the manner in which the survey is

conducted or scientific procedures used to aggregate the survey data), so are free of any hypotheticals that cannot be verified. For example, no information is necessary regarding fish ingestion rates for different individuals or different ethnic groups because the safe fish consumption rate is only governed by the RfD; it is this bright line that separates healthy fish consumption (consuming PCB-contaminated fish *below* the RfD) from fish consumption that can be toxic (eating PCB-contaminated fish in excess of the RfD). Because it is not necessary to assume what the fish ingestion rates are, fish advisories avoid contentious discussion on this issue. This is why state health departments, including DOH, rely solely on fish consumption advisories to protect the public rather than other types of health evaluations.

2. U.S. EPA HHRA: A risk assessment can also be conducted to estimate the health risks posed by eating PCB-contaminated fish. However, this type of risk assessment is typically conducted for enforcement action based on a single *hypothetical*, assumed fish consumer that is selected after the mathematical simulations to represent the population are complete.

Several DOH documents present the methodology for calculating the safe number of fish meals that can be eaten per month. All methods are based on the safe *daily* intake of PCBs, which is represented by EPA's RfD toxicity value of 0.00002 milligram/kilogram-day (mg/kg-day: the number of mg PCBs per kg body weight every day). In other words, as long as this daily PCB intake does not exceed the RfD, no significant toxic effects are expected. The fish consumption advisory simply allows toxicologists to determine the number of fish meals that can be eaten every month that will not exceed the RfD. EPA defines the RfD as:

> *Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.* [5]

Although the toxicological method for deriving an RfD is a multistep process starting with identifying the dose that causes toxicity in animal studies (from peer-reviewed scientific journals) and adjusting to account for species differences (extrapolating from laboratory animals to humans), the concept is easily explained with the following simple analogy. Aspirin (acetylsalicylic acid) is an analgesic (pain reliever) that also reduces inflammation (swelling of tissue and joints) and has been used worldwide for more than a century. It is sold as an over-the-counter (OTC; no prescription necessary), nonsteroidal anti-inflammatory drug (NSAID). This means that while many people use it, they must self-medicate

themselves and take care not to take more aspirin than the recommended daily dose. Because it is an OTC drug that is not prescribed by a physician, it is important that an individual knows the safe daily dose before taking it that. This safety information is clearly listed on the label (along with cautionary contraindications for children and preexisting medical conditions). The label states that each aspirin tablet is 325 mg and that the maximum number of tablets that should be taken is 12 tablets per day (24-hour period) which means that the safe daily intake is 3,900 mg/day (i.e., 12 tablets x 325 g-per tablet = 3,900 mg). In other words, if a person takes 12 aspirins per day (or less), no toxic effects are expected (exceeding this safe dose level could produce toxic effects like vomiting, tinnitus, confusion, hyperthermia, rapid respiration, metabolic acidosis, and multiple organ failure). [6] In other words, the safe daily intake dose on the label is simply the RfD for aspirin; although the RfD is referred to as a *toxicity value*, it is actually the bright line that separates a safe dose (dose lower than the RfD) from the toxic dose (greater than the RfD). The RfD is the safe dose that should not be exceeded.

The toxicological approach used by the pharmaceutical company (i.e., aspirin manufacturer) to calculate the safe daily aspirin dose is the same methodology used by EPA to develop the RfD for PCBs.

It should be noted that I specifically use the term *safe* dose in this report to describe the maximum chemical dose that that is not expected to cause toxicity. This issue can be cleared up by noting that when the daily chemical dose is below the RfD it is a safe dose, but when the daily dose exceeds the RfD, toxic effects may be manifest. Therefore, the RfD serves as the point of departure. For example, when a person suffering from muscle aches or fever takes 12 aspirin tablets per day, the drug effect is efficacious to treat those symptoms, and no toxicity is expected. However, if that self-medicating person takes more than the recommend amount of 12 tablets per day (thinking more is better), that person may experience toxic or lethal effects (medically referred to as *salicylate poisoning;* starting with nausea and vomiting, which may progress to include cerebral edema and coma, and can ultimately lead to cardiopulmonary arrest). [7] Therefore, a safe daily dose is defined as ≤12 aspirins, and a toxic dose is more than that number.

It must also be stressed that the underlying *assumption* of a safe daily dose—as defined by the RfD—for any chemical is that a person is not being exposed to other sources of that chemical. This is an important assumption to highlight for both aspirin and PCBs. Prior or concurrent chemical exposures often produce body burdens (the amount typically measured in blood sample) that are already high and close to toxic levels. These exposures may be unintentionally ignored or not immediately recognized, which can have dire toxic consequences. For example, if a person suffering from the flu takes aspirin to reduce fever and relieve muscle aches, but that person is also on prescribed drugs containing aspirin, that person could be

unintentionally poisoned by not knowing the other drugs contain aspirin (there are more than 60 common OTC and prescribed drugs containing aspirin [8]). If blood levels of aspirin from other medications were already high, taking aspirin tablets could cause a medical crisis. That is because the toxicological concern is the total body burden (in a clinical setting, body burden is based on *total* aspirin exposure with mild to severe salicylate poising being a concentration of 40–100 mg/dL). If a person taking aspirin is not aware of aspirin contained in other drugs he or she is taking, the results could be catastrophic. The same is true for PCB exposures, but neither DOH nor Dr. Keenan considers the fact that *all* U.S. citizens already have an existing PCB body burden [9] that has nothing to do with eating Spokane fish; from a toxicological perspective, the DOH fish consumption rates may be too high for certain individuals.

While the RfD is interpreted as the safe daily dose in calculating the maximum number of fish that can be eaten, it does not take into consideration the fact that the general population already has a preexposure body burden (prior to eating any PCB-contaminated Spokane River fish). The PCB levels in the general population are carefully measured with blood samples every two years by the U.S. Centers for Disease Control and Prevention (CDC). [9] As in the aspirin example, ingesting any *additional* PCBs from Spokane fish will simply add to the body burdens of the fish consumers. Therefore, even when DOH calculates the number of fish that can safely be eaten, the number should be considerably lower to account for the already-elevated PCB levels in some Spokane fish consumers. As I discussed in Volume 3 of my report, people who maintain a diet rich in fish (from any source) have been shown to have the highest PCB body burdens in the general population, so the RfD may not be a safe exposure for this particular group (even when they do not exceed the maximum number of DOH-recommended fish meals). In that group, PCB levels could accumulate to toxic levels without their knowing it because people do not typically monitor their PCB levels. This could pose medical issues for both toxic systemic effects and for significantly increasing their risk for cancer. I stress this point not because I am suggesting that DOH should adopt an alternative risk assessment approach, rather that the DOH fish advisories could underestimate health risks for PCBs for some groups (that already have high PCB body burdens and who do not know it) and not be protective for the entire fish-eating population. My opinion rebuts Dr. Keenan's opinion that the fish consumption advisories are overly protective; he has not considered preexisting PCB body burdens in his analysis.

As shown with the simple analogy above, calculating the number of PCB-contaminated fish that can be safely consumed is straightforward, easily understood, and can be determined for any chemical (for which a safe daily intake—the RfD—has been determined). It *does not* include knowing any more than 1) the chemical-specific RfD, and 2) the fish tissue contaminant level. Most importantly, it does not include any

hypothetical assumptions about fish consumption rates for average and upper-bound fish eaters or need to account for differences between the frequency of fish meals for different ethnic groups or those who eat subsistence levels of fish meals. In contrast, Dr. Keenan's HHRA is completely governed by these hypothetical daily fish consumption rates. None of this information is necessary with the U.S. EPA/DOH approach because it is solely based on the safe daily PCB dose (i.e., RfD)

In this sense, the DOH approach is completely free of any hypothetical or extraneous information. As such, it can be regarded as a straightforward toxicological analysis. Just like the aspirin label provides the necessary cautionary warning that more than 12 tablets per day may produce toxic effects, the DOH Fish Consumption Advisory provides easily understood toxicity information that is scientifically tenable.

It is also important to note that even when both the risk assessment and fish advisory calculation are based on the same fish species and fish PCB contaminant levels, the results and conclusions of the two types of health evaluations are in stark contrast. Whereas the risk assessment may indicate eating PCB-contaminated fish poses no risk (to the *assumed* exposed population), the fish advisory puts restrictions on the number and types of fish that can be safely eaten. It is not clear from Dr. Keenan's HHRA results and conclusions that the current PCB levels do not pose unacceptable risk, if he has also concluded that no restrictions or recommendations need to be developed for eating Spokane PCB-contaminated fish and fish consumers can eat any fish *ad libitum.* It is my opinion that DOH's fish consumption advisories are necessary, reasonable, and appropriate (and may actually underestimate the noncancer heath threat).

For the above reasons, I have primarily focused on the straightforward, scientifically tenable, and easily understood analysis that all toxicologists rely on: fish consumption advisories. This is because, described in its simplest terms, the fish consumption advisory sets a limit on how much PCB exposure is safe. Exceeding the number of recommended fish meals could have toxicological effects because safe PCB dose would be exceeded.

1.4. Dr. Keenan Critique: I Did Not Conduct an Independent Analysis of Current Health Risks

In Volume 3 of my expert report, I analyzed, reviewed, and summarized numerous ATSDR/DOH Health Consultations. I stated the purpose of that analysis, which was to evaluate the risk assessment methodology to determine if it was reasonable and scientifically tenable and also if it followed generally accepted toxicological practices. I concluded they did.

When I reviewed the ATSDR/DOH health consultations (pre-2012), they were consistent with many fish consumption advisories I have reviewed or participated in over the last couple of decades. When I evaluated the more recent DOH fish advisories [10] based on the 2012 DOH fish data, they followed the same procedures, and I concluded that DOH has continued to apply the same toxicological approach as the past evaluations and its findings and conclusions were correct.

In the following sections, I present a detailed analysis of the DOH fish advisory (using the 2012 DOH fish dataset) and apply the same methodologies and procedures detailed in the ATSDR/DOH consultations (post-2012). However, it should be noted that U.S. EPA/DOH fish risk assessment methodology has not changed over the last two decades, and it is not expected to undergo any changes in the future because it is based on bedrock toxicological principles that were developed many decades ago. For all my analyses, I rely only on the post-2012 DOH documents to be consistent with my independent analysis of the more recent 2012 fish tissue PCB levels.

I have identified the following three DOH fish consumption documents most pertinent to my opinion because they provide the most-detailed and relevant information for this case on this particular topic:

1. How Fish Tissue Data Is Used to Develop a Fish Advisory, SRRTTF Workshop, February 9, 2016. McBride, Office of Environmental Public Health Sciences, DOH. [11]
2. *Fish Advisory Evaluation Upper Columbia River Hatchery White Sturgeon 2017*., April 3, 2018. McBride, Division of Environmental Public Health Office of Environmental Public Health, DOH. [12]
3. *How DOH Develops Fish Advisories*. November 6, 2018. McBride, Office of Environmental Public Health Sciences, DOH. [10]

DOH uses the equation shown in Exhibit 5 and input parameters in Exhibit 6 for all their calculations. These can be directly use calculated the number of fish meals that are safe to each per month based on an average fish meal weight of 8 ounces or 227 grams. These fish consumption equations and parameters are only intended to protect Spokane fish consumers from developing *noncancer* or systemic organ toxicity and are all based on the RfD as was previously discussed.

Exhibit 5. Noncancer Fish Meal Equation Used to Develop DOH Fish Consumption Advisories [12]

Non-cancer meal equation:

$$Meal\ per\ month = \frac{RfD\ x\ BW\ x\ CF1\ x\ CF2}{MS\ x\ C}$$

Exhibit 6. DOH Parameters Used to Calculate Fish Consumption Rates [12]

Parameter	Value	Units	Comments	Source
Reference Dose (RfD)	Variable	mg/kg-day	Chemical specific	EPA IRIS or ATSDR MRL
Body Weight (BW)	60 or 70	kg	70 kg adult, 60 kg adult female	EPA Exposure Factors Handbook
Conversion Factor (CF1)	30.44	days/month		
Conversion Factor (CF2)	1000	g/kg		
Meal Size (MS)	227	g	8 oz. meal	DOH
Concentration in fish (C)	Mean contaminant concentration	mg/kg	Specific to species	EPA

These are relatively simple equations that don't requiring making hypothetical assumptions or complex mathematical models as Dr. Keenan has done. The only information necessary to make this calculation is the PCB RfD, which is 0.00002 mg/kg-day. All that needs to be done is to determine how many fish can be eaten so that the daily dose of PCBs in the fish does not exceed 0.00002 mg/kg.

It should also be noted that there are two daily intake toxicity values that can be used to calculate the fish consumption rate. The first, and generally used, source of safe daily intake values is the U.S. EPA Integrated Risk Information System (IRIS), which derives the RfD. The second is ATSDR, which derives Minimal Risk Levels (MRLs). [13] ATSDR takes a very similar approach in developing its MRLs, which are numerically very similar to RfDs. The MRL is defined by ATSDR [13] (which is similar to the U.S. EPA definition of an RfD cited above) as follows:

> *An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.* [13]

To develop its fish advisories, DOH used the chemical-specific toxicity values (RfDs/MRLs) shown in Exhibit 7:

Exhibit 7. DOH RfDs and MRLs Used to Calculate Current Fish Advisories Based on the 2012 Fish Tissue Data [10]

Chemical	Toxicity Value mg/kg-day	Source of Toxicity Value
PCBs	3E-5 2E-5	ATSDR MRL U.S. EPA
Methyl-mercury	1E-4	EPA IRIS
PBDE	1E-4	EPA IRIS

I have verified the toxicity values DOH used are consistent with the most current U.S. EPA IRIS or ATSDR RfDs/MRLs, which are presented in 0. However, DOH used the ATSDR MRL for PCBs that represents intermediate exposures (3x10-5) rather than for chronic exposures (2x10-5). [14]

Exhibit 8. Current Toxicity Values and Critical Effects for Chemicals of Concern in Fish Tissue [15] [16]

Chemical Name	**Toxicity Endpoint**	**Critical Effect or Tumor Type**	**Toxicity Value Type**	**Toxicity Value mg/kg-day**
PBDE-209	Cancer	Liver neoplastic nodules or carcinoma (combined)	Oral Slope Factor	7x10-4 [5]
PBDE-209	Noncancer	Neurobehavioral effects	RfD	7x10-3 [5]
PBDE-153	Noncancer	Neurobehavioral effects	RfD	2x10-4 [5]
PBDE-99	Noncancer	Neurobehavioral effects	RfD	1x10-4 [5]
PBDE-47	Noncancer	Neurobehavioral effects	RfD	1x10-4 [5]
Aroclor 1254		Ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails; decreased antibody (IgG and IgM) response to sheep erythrocytes	RfD	2x10-5 [5]
Polychlorinated biphenyls (PCBs)	Noncancer	Neurological	ATSDR/MRL Intermediate Exposures	3x10-5 [14]
Polychlorinated biphenyls (PCBs)	Noncancer	Immunological	ATSDR/MRL Chronic Exposures	2x10-5 [14]
Polychlorinated biphenyls (PCBs)	Cancer:B2 (Probable human carcinogen) - based on sufficient evidence of carcinogenicity in animals) (1986 guidelines)	Liver hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas	Oral Slope Factor	2 [5]
Methylmercury (MeHg)	Noncancer	Developmental neuropsychological impairment	RfD	1x10-4 [5]
Methyl-mercury (MeHg)	Noncancer	Developmental impairment	ATSDR/MRL Chronic Exposures	2x10-5 [14]

Notes:
ATSDR MRL [14]
U.S. EPA IRIS RfD, Slope Factor [5]

Thus, armed with just the RfD (and body weight of the average fish consumer), the number of monthly fish meals can be easily calculated for any species of contaminated fish for any section of the Spokane River.

1.5. DOH-Calculated Fish Consumption Recommendations

DOH has reviewed and analyzed the 2012 fish tissue sampling data and calculated the *mean* or *average* PCB concentration (which I have reviewed and found to be representative). [17] [18] [19] Their calculated mean concentrations and calculated maximum fish consumption rates for each select fish species are presented in Exhibit 9. [10]

Exhibit 9. 2012 DOH Mean Fish Tissue Concentrations and Corresponding Maximum Fish Meal Monthly Rates [10]

2018 Assessment – Cumulative Effects

Calculated Meal Limits Assuming 50% Reduction in Organics

Species	PCB sampling data		PBDE sampling data		Mercury sampling data		Combined	Recommendations*
	Mean PCB Aroclor Conc. (ug/kg ww)*	PCB Aroclor Meals/Month*	Mean PBDE Conc. (ug/kg ww)*	PBDE Meals/Month*	Mean Hg Conc. (ug/kg ww)	Hg Meals/Month	Meals/Month*	Recommendation for both PCBs, PBDEs, & Hg*
Spokane Arm								
Largescale sucker (whole)	113.8	1.6	123.3	6.5	60.3	13.3	1.4	1
Brown Trout (fillet)	33.3	5.6	30.4	26.5	85.4	9.4	3.6	4
Rainbow Trout (fillet)	28.8	6.5	8.5	94.7	49.6	16.2	5.2	4
RM 33.7 - Little Falls Pool								
Largescale sucker (whole)	33.0	5.7	20.4	39.5	39.0	20.6	4.8	4
Northern Pikeminnow (fillet)	25.9	7.3	8	100.6	147.0	5.5	3.3	4
RM 56.6-57.1 - Upper Lake Spokane								
Largescale sucker (whole)	126.0	1.5	102.6	7.8	55.3	14.5	1.4	1
Mt whitefish (fillet)	81.6	2.3	159.0	5.1	30.7	26.2	1.7	2
Northern Pikeminnow (fillet)	53	3.5	31.8	25.3	157.0	5.1	2.2	2
Rainbow Trout (fillet)	43	4.4	32.7	24.6	44.1	18.2	3.7	4
RM 64 & 77 - Nine Mile Dam to Up River Dam								
Largescale Sucker (whole)	63.0	3.0	64.1	12.6	25.0	32.2	2.7	2
Mt whitefish (fillet)	125.0	1.5	417.2	1.9	50.0	16.1	0.9	1
Rainbow Trout (fillet)	49.3	3.8	93.4	8.6	36.9	21.8	2.7	2
RM 84.4 & 96 - Upriver Dam to Border (Note: WDFW has closed this area - Catch and Release Only)								
Largescale Sucker (whole)	75.1	2.5	67.0	12.0	46.4	17.3	2.2	2
Northern Pikeminnow (fillet)	21.6	8.7	5.9	136.6	185.0	4.3	3.1	4
Rainbow Trout (fillet)	29.9	6.3	27.7	29.0	36.5	22.0	4.9	4

DOH has had to make some difficult decisions (as all state health departments do) about what type of fish data to use in its Fish Consumption Advisories. DOH has made the reasonable public health decision to use 50% of the detected PCB concentration based on the assumption that 50% of the PCBs will be removed during fish preparation and cooking. While I concur this is a reasonable risk management decision (which is based on a qualitative balance of benefit-risk), the U.S. EPA Fish Advisory [2]

suggests using the full detected concentration to account for those who do not follow the DOH fish advisory recommendations, stating:

> *Analysis of skinless fillets may also be more appropriate for some target species such as catfish and other scaleless finfish species. In contrast, using whole fish with skin-on as the sample type for assessing PCBs, dioxins/furans, or organochlorine pesticide exposures in populations of Native Americans, Asian Americans, Caribbean-Americans, or other ethnic groups that consume whole fish in a stew or soup is warranted because these contaminants accumulate in fatty tissues of the fish. Cooking the whole fish to make a stew or soup releases the PCBs, dioxins/furans, or organochlorine contaminants into the broth; thus, the whole fish should be analyzed to mirror the way the consumer prepares the fish. Similarly, using skin on fillets with belly-flap included for most other scaled fish to evaluate PCB, dioxin/furan, or organochlorine pesticide exposures in the general fishing population or among recreational fishers is appropriate since this is a standard filleting method (see Sections 7.2.2.6 and 7.2.2.7). This method also allows for the inclusion of the fatty belly flap tissue and skin in which organochlorines, PCBs, and dioxins/furans concentrate and takes into account the fact that some consumers may not neatly trim the more highly contaminated fatty tissue from the edible muscle fillet tissue.* [2]

Exhibit 10 shows the number of fish meals corresponding to the fish tissue levels calculated by U.S. EPA and presented in its 2000 fish guidance document. [2] This is important in this case because the DOH-calculated PCB fish consumption advisories Dr. Keenan has critiqued have been used and applied at numerous sites for two decades. Although the U.S. EPA fish consumption rates presented are slightly different from the DOH levels, they were calculated the same way and provide the same number of fish meals. In all respects, they provide the same calculated number of fish meals. The only difference is the manner in which the fish data are presented. While the U.S. EPA numbers present ranges of PCB fish concentrations that correspond to the number of meals, the DOH table presents similar numbers of meals for a specific fish concentration. For example, U.S. EPA calculated that when the fish tissue PCB concentration is between 16 and 23 ppb (note the units in the table are in ppm and have been converted), the maximum number of fish meals is 8. (See Exhibit 10.) A comparison of this result to the DOH table (Exhibit 9) presents a similar result. This is similar to that shown for Northern Pikeminnow at RM 84.4 & 96, as that fish sample had a fish tissue PCB concentration of 21ppb, which falls in the U.S. EPA range of 16–23 ppb; DOH calculated the same number of fish meals that could be eaten. The only reason U.S. EPA could not construct a table identical to the one DOH prepared is because U.S. EPA did not have actual sampling data and, therefore, published a table with bracketed fish tissue PCB concentrations. On the other hand, DOH was able to be very detailed and calculate the specific number of meals based on a specific fish tissue PCB concentration. Both U.S. EPA and DOH used the same equations and the same RfD value.

In addition, the U.S. EPA table presented in 0 provides monthly fish consumption rates for fish tissue PCB based on cancer risk, which are much more restrictive. For example, when the fish tissue PCB concentration exceeds 94 ppb, as indicated in the table, no fish should be eaten. Applying this value to screen the DOH data in Exhibit 9 shows that there would be a total ban on eating three fish. However, 94 ppb represents a risk level corresponding to 1E-5 (as described in the table notes) and not to the *de minimis* cancer risk level of 1E-6. If the U.S. EPA table were adjusted to correspond to a *de minimis* bright line of 1E-6, the fish PCB concentration would be 9.4 ppb; when this risk-based tissue PCB level was compared with the DOH table, there would be a total ban on eating any fish from any site in the Spokane River. Finally, as discussed above, the concentrations presented in the DOH table represent only 50% of the fish PCB concentration that was actually detected.

Exhibit 10. U.S. EPA PCB Fish Consumption Calculations: Presented Fish Risk Assessment 2000 Guidance [2]

Table 4-24. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - PCBs

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.0059	0 - 0.0015
16	>0.0059 - 0.012	>0.0015 - 0.0029
12	>0.012 - 0.016	>0.0029 - 0.0039
8	>0.016 - 0.023	>0.0039 - 0.0059
4	>0.023 - 0.047	>0.0059 - 0.012
3	>0.047 - 0.063	>0.012 - 0.016
2	>0.063 - 0.094	>0.016 - 0.023
1	>0.094 - 0.19	>0.023 - 0.047
0.5	>0.19 - 0.38	>0.047 - 0.094
None (<0.5)	>0.38	>0.094

In summary

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.
* Concentration reported in parts per quadrillion (nanogram per kg or 10-9 g/kg.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, and RfD of $2x10^{-5}$, and a cancer slope factor (CSF) of 2 $(mg/kg\text{-}d)^{-1}$.
2. NONE = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for PCBs (sum of Aroclors) is 2×10^{-2} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

In summary, the DOH fish consumption rate results are supported by U.S. EPA's results that were calculated approximately 20 years ago. DOHs values are as scientifically valid today as they were then. If DOH's fish consumption rates were based on a *de minimis* cancer endpoint, there would be a total ban on eating any fish caught at any point in the Spokane River.

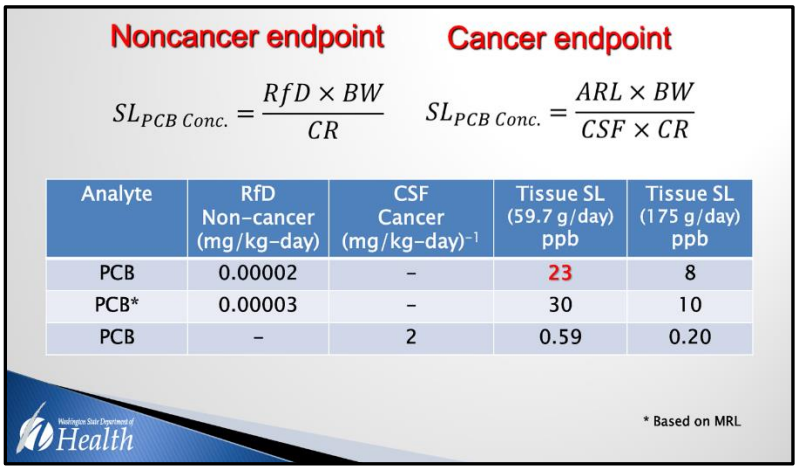
1.6. DOH *De Minimis* Fish Tissue PCB Concentrations

As discussed previously, the U.S. EPA has calculated *de minimis* fish tissue PCB concentrations. While DOH relies solely on the noncancer systemic toxicity endpoint represented by the RfD, it has also calculated the fish PCB tissue level that corresponds to a *de minimis* cancer risk.

These two fish tissue concentrations represent bright lines for evaluating and interpreting the fish tissue data. That is, when the fish tissue concentration is below the *de minimis* concentration defined by the RfD, there should be no concern about potential noncancer systemic toxicity. Likewise, fish tissue samples below the *de minimis* PCB tissue concentrations for cancer will not pose a noncancer health threat nor a significant risk of developing cancer (because the cancer fish tissue concentration is much lower than the noncancer value).

Like U.S. EPA, DOH has calculated the *de minimis* fish tissue PCB consumption rates and the corresponding fish consumption rates. (See Exhibit 11.) However, DOH calculated these values based on the average and upper-bound fish consumption rates of 59.7 and 175 g/day, respectively.

Exhibit 11. DOH Fish Tissue PCB Concentrations: Corresponding to *De Minimis* Cancer Levels for Average and Upper-Bound Fish Consumers [10]



As previously discussed, *de minimis* PCB concentrations are based on the safe daily intake of PCBs, which is the RfD for noncancer health effects, or a 1E-6 cancer risk level. DOH only relies on the noncancer toxic endpoint for its fish consumption advisories.

For this reason, it should be stressed that these advisories will not protect Spokane fishermen from elevated cancer risk. DOH shows this separately as another health outcome (Exhibit 11); because of a risk management decision, DOH does not consider cancer risk in the fish consumption advisories. This is because the PCB contaminant levels in fish would have to be significantly reduced from current (2012 PCB levels) to 0.59 and 0.2 ppb for the average and upper-bound fish consumer, respectively, to be protective against cancer at a *de minimis* risk level of one-in-a-million or 1E-6 cancer risk level. All 2012 fish tissue PCB levels far exceed these cancer levels. Indeed, it is clear from the DOH *de minimis* cancer risk levels calculated for PCB-contaminated fish that DOH would have to issue a total fish consumption ban, even when based on fish tissue data that had already been reduced by 50%.

DOH has chosen to calculate the mean fish tissue PCB concentration by assuming 50% of the original PCB concentration will be lost during preparation of the fish meal (removing the skin and cooking). This assumption seems reasonable and may be valid for the typical sport fisherman. Although this assumption will likely be representative of many fish consumers, it does not address the entire population of Spokane River fish consumers, including those who do not understand the fish advisories or because of traditional or ethnic differences in how different groups cook fish. In these cases, assuming a 50% reduced fish consumption concentration would significantly overestimate the number of fish that can be eaten, which could lead to toxic outcomes. That is, for groups who eat the fish whole (as U.S. EPA recommends is assumed), they could be ingesting *twice* the safe amount of PCBs and exceed the RfD by two-fold. Put another way, when interpreting the DOH fish meal recommendations, those who intend to eat the whole fish or who prefer to add the cooked residue oil to their meal should divide the DOH Fish Consumption Advisory by 50%.

My opinion that PCB-contaminated fish may pose health risks to some ethnic groups—even when they do not exceed the maximum allowable number of fish meals—is supported by DOH fish consumption surveys. For example, fish consumers in the Russian community report that an assumption of 50% concentration reduction may not be appropriate for them because they may not remove the skin or cook the fish, and they may eat it whole (minus the head and entrails). Spokane Regional Health District states in its 1998 *Fish Consumption Survey Spokane River, Washington:* [20]

> *Respondents identified five ways in which they prepare the fish from the Spokane River to eat: cutlets (ground fish-cakes), fried, dried, fish soup, and pickled (herring). The cutlets are prepared by grinding the fish after removal of head and spine; the tiny bones are included in the cutlets. It was reported that a common method to prepare sucker fish to eat was to make cutlets with them. To dry the fish, respondents report, the fish are salted while raw and then dried; they are never*

> *cooked. The whole fish is used when it is dried excluding the intestines and the head. Fish soup is prepared in different ways. Some people use the head others do not. The herring is pickled fish that is stored in a jar and does include bones.* [Emphasis added] [20]

It should also be noted that PCBs are virtually indestructible and are not destroyed by cooking (at normal cooking temperatures). Based on professional experience, this fact is contrary to opinions held by some in the general public (expressed to me in many public hearings). Unless the PCB-contaminated fat/oil is decanted off the cooking pan after cooking, the fish advisories will not be health effective in reducing PCB levels. Many fish consumers I have spoken to over the decades at contaminated sites believe the fish oil contains the very nutrients (like omega-3 fat) that they are loath to discard because they (correctly) believe the fish oil is the healthiest part of the fish (fish oil is sold as supplements in capsules and is a very popular nutritional supplement, with a market valued at $33.04 billion in 2016 [21]) . Some use cooked fish oil to season other parts of their meal or simply pour the oil back over their fish fillet (based on personal interviews). It should be noted that while the DOH Fish Consumption Advice presented in Exhibit 11 does *recommend* eating fish fillets and cooking the fish "so that the fat drips off," it does not include a statement that consumers should be sure to discard the oil after cooking. It also should also be noted that DOH recommends eating a healthy diet of fish that consists of two fish meals a week. However, a cursory glance at the DOH fish advisory table (Exhibit 9) shows this is not possible due the PCB contaminant level. As the table shows, there is no fish for which it is safe to eat two fish meals per week.

Exhibit 12. DOH Fish Consumption Advice [10]

General Fish Consumption Advice

DOH encourages all Washingtonians to eat at least two fish meals per week as part of a heart healthy diet in accordance with American Heart Association (AHA) recommendations. People may eat fish more than two times weekly, but such frequent consumers should take steps to reduce exposure to contaminants in the fish that they eat by following some general advice.

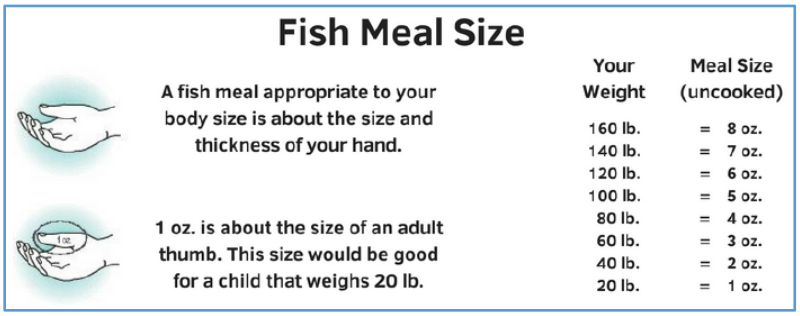
- Eat a variety of fish that are low in contaminants according to guidance provided on the DOH website at http://www.doh.wa.gov/fish/.
- Follow advice provided by DOH and other local health agencies on water bodies to fish.
- Young children and small adults should eat proportionally smaller meal sizes.
- Eat fillets without the skin.
- Consume younger, smaller fish (within legal limits). These fish typically contain lower levels of accumulative contaminants like PCBs and mercury than older, larger fish.
- When cleaning fish, remove the skin, fat, and internal organs before cooking; this will help to reduce the amount of some contaminants.
- Grill, bake, or broil fish so that fat drips off while cooking.

There is evidence that some in the general population do not cook their fish or they eat the entire fish; both of these cases would *not* result in a reduction of the fish tissue concentration by 50%. Although the health goal should be unlimited fish consumption (*ad libitum* fish consumption), this goal is not practical or likely to be achievable for the near future. Therefore, from a health perspective, the most useful and toxicologically meaningful benchmark for the general population who eat Spokane River fish should correspond to how many fish meals are recommended by health professionals and dieticians. There is a consensus among all health professionals that eating fish is vital to maintaining good health, as stated by Washington State DOH:

> *Fish is a low-fat high quality protein. Fish is filled with omega-3 fatty acids and vitamins such as D and B2 (riboflavin). Fish is rich in calcium and phosphorus and a great source of minerals, such as iron, zinc, iodine, magnesium, and potassium. The American Heart Association recommends eating fish at least two times per week as part of a healthy diet. Fish is packed with protein, vitamins, and nutrients that can lower blood pressure and help reduce the risk of a heart attack or stroke.* [2]

DOH also provides a helpful visual aid [2] to show the adjusted body-weight amount (fish tissue weight) that represents a typical fish meal. (See Exhibit 13.) (Fish consumption advisories are typically based on the average adult weight of 60 or 70 kilograms—132 or 150 pounds for women and men, respectively. The calculations I presented in this rebuttal report are based on these two average adult weights.)

Exhibit 13. DOH Weight Adjusted Meal Size [22]



While the FDA; U.S. EPA; and the National Academy of Sciences, Institute of Medicine (NASIOM) recommend a *minimum* of 8–12 ounces of fish per week (4 meals per month) for the average adult, [2] it is also necessary to consider those who eat more than the minimum number of fish meals. That is, when setting a benchmark or bright line for the number of fish meals that would show PCB levels have been reduced to *de minimis* levels, the number of fish meals needs to be considered, and the number of fish meals must be protective of most of the general population of the general population of Spokane fish consumers, especially those that eat the most fish. That is, while the recommended *minimum* number of fish meals (minimum of 4 per month) there is a sizable portion of the general population that eats Spokane in much greater amounts. That is, the goal is not limited to just protecting the average sport fisherman. The number of meals corresponding to *de minimis* health effects must consider ethnic groups who consume much more Spokane River fish than the average consumer, as well as those groups who rely on subsistence quantities of fish.

1.7. Calculated Fish Consumption Rates for PCB-Contaminated Fish: Full PCB Concentration and 50% Concentration Reduction

To address this credible scenario that some fish consumers will not follow the DOH fish advisories that will reduce the PCB concentration by 50%, I have calculated the maximum number of fish meals to represent Spokane fish consumers who do not cook their fish and/or do not discard the PCB-contaminated fish oil after cooking, as well as those who do. This is of real concern because DOE fish consumption surveys indicate that some groups do not prepare their fish meals in accordance with DOH recommendations. For example, DOE states in its 2013 Fish Consumption Survey: [23]

> *This telephone survey is part of a broader public outreach and education effort by the Lands Council directed to low-income families, indigenous people, and recent immigrant populations*

> *(Hmong, Vietnamese, Slavic, and Hispanic populations). Selection of these populations was based on previous work conducted by the Spokane Regional Health District, and State Departments of Health and Ecology, and suggests these ethnic populations may be at potential health risks from exposure to contaminants in fish harvested from the Spokane River.*
>
> *There are a significant number of people catching and/or eating fish from the Spokane River. For those eating fish, few are taking precautionary measures in preparation of the fish.*
>
> - *19 percent of respondents fish in the Spokane River.*
> - *12 percent catch and eat fish. Over half eat two or more fish in months they are regularly fishing.*
> - *Of those who said they eat fish from the Spokane River in a typical year, nearly two-thirds (65%) took no precautions in how they prepared the fish for cooking.*
> - *The majority of fishing that includes eating what is caught takes place below Long Lake Dam (80%), where there are no fish advisories regarding consumption.*
> - *Some fish consumption not in accordance with the Washington Department of Health fish advisory is occurring between Lake Spokane and the Idaho Border.* [23]

Furthermore, DOH has determined that the average and the upper-bound *daily* fish consumption rates are 59.7 and 175 g/day, respectively. These figures represent a *monthly* fish consumption rate of approximately 8 and 23 meals per month, respectively. Therefore, I use these bright-line consumption rates in my calculations below to interpret and characterize fish consumption to determine whether the monthly calculated fish consumption equals the average and upper-bound fish consumption rates. For example, the *maximum number* of fish meals that can be consumed for any of the PCB-contaminated fish listed for the 2012 fish tissue levels in the DOH Fish Consumption Advisory is 8.7 meals per month for Northern Pikeminnow at the Upriver Dam to the Idaho border. (See Exhibit 14.) At first glance, this could be interpreted to be a considerable number of fish meals, but this needs to be put into context of the average and upper-bound fish consumer; 8.7 fish meals per month is just slightly more than the average fish consumer (8 meals per month) and far below the upper-bound fish consumer (23 meals per month). All other calculated fish consumption rates (0) are below the average fish consumption rate of eight meals per month and well-below the upper-bound rate.

Moreover, the calculated 8.7 meals per month is based on the assumption that the fish tissue PCB concentration will be reduced by 50%. As previously noted, this assumption may not be justified for some groups.

Exhibit 14 presents the 2012 DOH fish data (which I have reviewed and verified) for the full detected PCB mean fish concentrations and the mean concentrations assuming a 50% reduction in edible fish tissue. The corresponding numbers of fish meals are shown for both datasets. This comparison addresses the risks associated with not preparing the fish meal in line with DOH recommendations.

As discussed previously, the maximum number of fish meals that would be safe to eat is solely based on the safe daily consumption rate (RfD). What is noteworthy is that only one out of 15 fish species analyzed from the five sampling locations was low enough that the average fish consumer could eat the *de minimis* number of fish meals. For the upper-bound fish consumer, the results clearly show that the number of fish meals fall far below the *de minimis* number of fish meals they would eat. In short, Spokane River fish are so contaminated with PCBs that the vast majority of fish could not be eaten anywhere close to the average and upper-bound consumption rates when fish consumers do not prepare their fish meals in accordance with the DOH recommendations (i.e., remove the skin, cook the fillet, and discard the oil).

Exhibit 14. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals PCB-Contaminated Fish *With* and *Without* Recommended Fish Meal Preparation

River Section	Fish Species	PCB Results Assuming 50% Reduction in PCB Concentration		PCB Results No Reduction in PCB Concentration	
		50% Mean PCB Aroclor Conc. (ug/kg ww)	PCB Aroclor Meals/Month	Total Mean PCB Aroclor Conc. (ug/kg ww)	PCB Aroclor Meals/Month
Spokane Arm	Largescale sucker (whole)	113.8	1.6	227.6	0.8
	Brown Trout (fillet)	33.3	5.6	66.6	2.8
	Rainbow Trout (fillet)	28.8	6.5	57.6	3.3
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	5.7	66	2.8
	Northern Pikeminnow (fillet)	25.9	7.2	51.8	3.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	1.5	252	0.7
	Mt whitefish (fillet)	81.6	2.3	163.2	1.1
	Northern Pikeminnow (fillet)	53	3.5	106	1.8
	Rainbow Trout (fillet)	43	4.4	86	2.2
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	3.0	126	1.5
	Mt whitefish (fillet)	125	1.5	250	0.7
	Rainbow Trout (fillet)	49.3	3.8	98.6	1.9
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	2.5	150.2	1.2
	Northern Pikeminnow (fillet)	21.6	8.7	43.2	4.3
	Rainbow Trout (fillet)	29.9	6.3	59.8	3.1

Notes:
DOH 2012 Data [17]
Assuming BW=70 kg; U.S. EPA RfD=0.00002
Orange Highlight = Average *de minimis* fish consumption rate of 8 meals/month

Additionally, as I discussed in Volume 3 of my expert report, PCB health risks are based on, and are proportional to, the PCB concentration. For example, a reduction in the PCB loading to the river producing a 10% reduction in fish tissue PCB concentrations will reduce the calculated health risk by 10%. This relationship also holds for the fish consumption advisory shown in Exhibit 14. For example, in the first row, the number of largescale sucker meals for the full PCB concentration is 0.8, while the number of meals is doubled to 1.6 meals for the same fish assuming the PCB concentration is 50%.

1.8. Calculated Fish Consumption Rates for PBDE-Contaminated Fish

Dr. Keenan critiqued my report because he stated that I ignored other contaminants.

In addition to PCBs, fish have been shown to be contaminated with polybrominated diphenyl ethers (PBDEs), which are flame retardants used in a variety of consumer and industrial products [24] and are complex mixtures of 209 individual PBDE congeners. The 2012 fish sampling data include individual sampling results for 13 PBDE congeners (i.e., PBDE-049, -066, -071, -138, -153, -154, -183, -184, -191, -209, -047, -100). U.S. EPA has developed RfDs for four PBDE congeners.

DOH has calculated the mean PBDE concentrations for fish tissue, as shown in Exhibit 15. (I have reviewed these and find they are representative of PBDE fish contamination levels). Based on the mean concentration, I calculated the number of fish meals per month fish consumers could eat without experiencing toxic effects.

What is noteworthy about these results in comparison with Exhibit 14 is that, because PBDE is much less toxic than PCBs, many more fish meals can be eaten when comparing PBDE to PCBs. (The U.S. EPA RfDs for PCBs and PBDE are 0.00002 and 0.0001, respectively, making PCBs five times more toxic than PBDEs). It should be noted that the PBDE concentrations, like the PCB concentrations above, have been reduced by 50%, so this comparison is an "apple-to-apple" comparison to above PCB numbers presented in column 2 of Exhibit 14.

As shown in Exhibit 15, the average Spokane fish consumers can eat the *de minimis* number of fish meals for some species at *all* five fish sampling locations. For specific fish species, the highlighted (orange- plus green-shaded) boxes show that 11 out of 15 (73%) of the fish sampled at the five locations can be eaten at *de minimis* average fish consumption rates (8 meals/month). Moreover, the table also shows that the PBDE levels are sufficiently low that, even for upper-bound fish consumers (23 meals/month), 8 out of

the 15 fish (more than half or 53%) samples are below toxic levels and they can eat the number of *de minimis* number of fish meals.

These results are in stark contrast to the PCB results shown in Exhibit 14 in which there was only one species at one location where tissue PCB concentrations would permit average fish consumers to eat *de minimis* amounts of fish tissue (assuming 50% PCB concentration reductions, as were assumed here for PBDE).

Exhibit 15. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals—PBDE-Contaminated Fish

River Section	Fish Species	PBDE Results Assuming 50% Reduction in PBDE Concentration	
		Mean PBDE Conc. (ug/kg ww)	PBDE Meals/Month
Spokane Arm	Largescale sucker (whole)	123.3	6.5
	Brown Trout (fillet)	30.4	26.4
	Rainbow Trout (fillet)	8.5	94.5
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	20.4	39.4
	Northern Pikeminnow (fillet)	8	100.4
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	102.6	7.8
	Mt whitefish (fillet)	159	5.1
	Northern Pikeminnow (fillet)	31.8	25.3
	Rainbow Trout (fillet)	32.7	24.6
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	64.1	12.5
	Mt whitefish (fillet)	417.2	1.9
	Rainbow Trout (fillet)	93.4	8.6
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	67	12.0
	Northern Pikeminnow (fillet)	5.9	136.2
	Rainbow Trout (fillet)	27.7	29.0

Notes: DOH 2012 Data McBride [10]
Assuming BW=60 kg; U.S. EPA RfD=0.0001
Green Highlights = Upper-bound *de minimis* fish consumption rate 23 meals/month
Orange Highlights = Average *de minimis* fish consumption rate 8 meals/month

1.9. Calculated Fish Consumption Rates for Mercury-Contaminated Fish

Like PBDEs discussed above, Spokane fish are also contaminated with Hg. However, unlike PCBs and PBDE, Hg is a not a manufactured commercial synthetic contaminant. It has a Statewide ubiquitous distribution and is correctly characterized as an environmental background chemical. It is both a naturally occurring background element present in rock and soils and is also an anthropogenic background chemical (released from man's activity, often from fuel combustion). It is largely an airborne contaminant (that crosses state boundaries) that contaminates water bodies as a result of deposition and subsequent surface runoff into water bodies. Spokane River fish have been found to contain Hg.

Exhibit 16 shows the DOH mean Hg concentration for the same fish that were analyzed for PCBs and PBDEs (Exhibit 14 and Exhibit 15). The major difference between PCBs and PBDE, and Hg, is that PCBs and PBDEs are primarily stored in fish fat tissue, while Hg is not. Hg is largely bound to proteins in fish muscle tissue rather than to fat, so cooking has no effect on reducing the Hg concentration. The major chemical form of Hg in fish tissue is methyl-mercury, which is the bioaccumulative form of Hg (elemental Hg is not typically bioaccumulated). Accordingly, the Hg concentrations presented in Exhibit 16 represent the full laboratory Hg concentrations.

I have conducted the same analyses on the Hg fish tissue results as I described above for PCBs and PBDEs. That is, I assumed Hg is the only contaminant present in fish tissue in order to isolate Hg and determine the number of fish meals that can be eaten solely attributable to this one contaminant.

The results for Hg are strikingly similar to those I discussed for PBDE-contaminated fish above. Again, some fish species can be eaten at *de minimis* fish consumption rates for <u>all</u> sections of the river. Twelve fish samples out of 15 (80%) had Hg levels low enough to permit the average fish consumers to consume the *de minimis* number of fish meals (8 meals/month). For the upper-bound fish consumer (23 meals/month), two fish samples (2/15) had Hg levels low enough to allow *de minimis* fish consumption. However, it should be noted that, while the number of fish samples for upper-bound *de minimis* fish consumption were less than I showed and discussed above for PBDE (8/15), the Hg fish concentrations for many samples were well above the <u>average</u> *de minimis* levels. For example, three fish samples had Hg levels that would allow more than 20 meals per month, and the rest were also well above the average *de minimis* average rate of eight meals per month.

Exhibit 16. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals—Hg-Contaminated Fish

River Section	Fish Species	Mean Hg Conc. (ug/kg ww)	Hg Meals/Month
Spokane Arm	Largescale sucker (whole)	60.3	13.3
	Brown Trout (fillet)	85.4	9.4
	Rainbow Trout (fillet)	49.6	16.2
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	39.0	20.6
	Northern Pikeminnow (fillet)	147.0	5.5
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	55.3	14.5
	Mt whitefish (fillet)	30.7	26.2
	Northern Pikeminnow (fillet)	157.0	5.1
	Rainbow Trout (fillet)	44.1	18.2
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	25.0	32.1
	Mt whitefish (fillet)	50.0	16.1
	Rainbow Trout (fillet)	36.9	21.8
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	46.4	17.3
	Northern Pikeminnow (fillet)	185.0	4.3
	Rainbow Trout (fillet)	36.5	22.0

Notes: DOH 2012 Data McBride [10]
Assuming BW=60 kg; U.S. EPA RfD=0.0001
Green Highlights = Upper-bound *de minimis* fish consumption rate 23 meals/month
Orange Highlights = Average *de minimis* fish consumption rate 8 meals/month

1.10. Dr. Keenan Stated I Ignored Lead as a Contaminant

The last contaminant Dr. Keenan stated I ignored was lead (Pb). I did not ignore it. I conducted a toxicological analysis of Pb, but did not include it in my report because it is not possible to quantitatively evaluate it like I did for PCBs, PBDE, and Hg for the simple reason that Pb does not have an RfD. Neither U.S. EPA nor ATSDR has developed an RfD for Pb. Therefore, it cannot be evaluated together with the other three contaminants.

As I have discussed, both U.S. EPA and DOH fish risk assessment guidance presents the same equation for evaluating and quantifying the risks and safe fish consumption rates for multiple contaminants. (See Exhibit 17). [2] [12] In fact, this is the exact equation that DOH used to evaluate Spokane River fish (for the 2012 DOH data), and it was used just as presented to support the current Fish Consumption Advisory; it is obvious that Pb was not included in DOH's quantitative analysis.

Exhibit 17. DOH Equation for Calculating the Risks and Fish Consumption Rates for Multiple Contaminants [12]

$$Meals\ per\ month = \left(\frac{BW \cdot CF}{MS}\right) \cdot \left(1 / \left(\left(\frac{C_{mercury}}{RfD_{mercury}}\right) + \left(\frac{C_{PBDE}}{RfD_{PBDE}}\right) + \left(\frac{C_{PCB}}{MRL_{PCB}}\right)\right)\right)$$

It should be noted that the first consumption advisory was intended to warn the public about the number of meals that were safe to eat in terms of both PCBs and Pb. It focused on the same fish species that were sampled in the 1999 U.S. Geological Survey (USGS)/Washington State DOH report—namely, rainbow trout, mountain whitefish, and largescale suckers. The warning for Pb exposures only seems to have been applied as a precautionary note for consuming the "nonedible" parts of the fish and was thus issued for eating the whole fish. However, this was based on the specific wording of the one-page Fact Sheet and the supporting 1999 USGS and other fish data, since I was unable to locate the entire 2001 Washington State DOH Health Advisory. [25]

While the fish advisory applied to both whole fish and fillets for PCB contamination, the Health Advisory (which appears to err on the side of caution) also noted that there was a potential health threat from Pb-contaminated fish, but only applied to consuming whole fish" for Pb. It did not apply to fish fillets, as stated in the following section of the Health Advisory:

> *What are the harmful effects of PCBs and lead? Who should be concerned? Pregnant women and women considering pregnancy should carefully follow the meal limits given in table 1.*
>
> *The fetus is particularly susceptible to the harmful effects of lead and PCBs when the mother eats contaminated fish. Such effects can include learning problems that appear during childhood years. Negative effects on a child's behavior and ability to learn can also occur in children exposed to lead from birth through six years of age.* ***Because lead was found at higher levels in whole fish samples, it is especially important for children under age six to eat only fillets according to the meal limits in table 1.*** [original emphasis] [25]

As the Health Advisory emphasis indicates, Pb was only a concern when consuming whole fish. The reason for this distinction is that, unlike PCBs, which are bioaccumulated in all fat-containing tissues and organs in fish, Pb is not. After Pb is absorbed by fish, it is sequestered and stored in nonedible fish parts like the gills, bone, kidney, spleen, and intestines, but the bone is the most likely It is largely sequestered into bone, where it substitutes for calcium. This type of absorption and sequestration into bone is similar to how the human body stores Pb. Consequently, and most importantly, Pb does not bioaccumulate in fish muscle tissue, so the only concern with Pb in typical fish advisories pertains to eating the whole fish—including bone and gills. This opinion is supported by the detailed analysis later addressed and carefully analyzed in the 2007 ATSDR/Washington State DOH Health Consultation for Spokane River fish in which a determination was made to eliminate Pb as a chemical of concern, as it was shown that consuming fish fillets would not pose a health threat (i.e., muscle tissue fillets contain 10 times less Pb than the nonedible whole-fish body parts). [26]

With regards to lead, Washington State DOH issued advice against eating whole fish because USGS studies showed fish fillets from Spokane River fish did not bioaccumulate Pb—even those fish caught in river areas known to be highly enriched with Pb-laden mining waste. The 1989 USGS study (Maret and Skinner 1989; published 2 years before the 2001 Health Advisory) showed fish analyzed from Spokane River sections known to be downstream of mining production sites had insignificant bioaccumulation of any heavy metal, including Pb, in fillet muscle tissue. In fact, the USGS showed there was a "poor correlation" between the paired highly contaminated heavy metal sediments in mining areas (save for Cd) and the corresponding fish tissue levels in those areas. USGS stated:

> *Correlations between most trace-element concentrations in bed sediment and tissue (livers and fillets) were poor; however, there was a significant correlation between Cd in bed sediment and liver tissue. Trace-element concentrations in bed sediment did not appear to be good predictors of concentrations in tissue…* [25]

In addition to discussing the very important concept that heavy metals did not bioaccumulate in fish, work by USGS (1989) showed that the fish tissue levels—even in highly enriched sediments—were below the U.S. EPA sediment screening values (SV) that were developed for bed sediments and edible fish tissue. (SVs were defined as "associated adverse effects to aquatic life or human health are possible, but expected infrequently"; USEPA tissue SVs were protective of human health at a "1 x 10-5 risk factor" based on an average-sized adult (70 kilograms) and a consumption rate of 6.5 grams of fish per day (or approximately 45 grams of fish per week). USGS stated:

> *Even though many of the sites exhibited trace-element enrichment, no trace-element concentrations in sportfish fillets exceeded USEPA SVs. This is noteworthy, because Pb and Hg can bioaccumulate in aquatic biota and are pollutants of concern around mining sites in the study area. It is apparent from this study that trace elements in bed sediment are not readily bioavailable for uptake by fish, especially the trace elements As, Cd, Pb, Hg, and Se, which are known to bioaccumulate in aquatic food chains.* [25]

Finally, even in areas in which the riverbed Pb sediments were greatly enriched to levels higher than 100 ppm, no Pb bioaccumulation was seen in fish livers or fillets:

> *Although concentrations of Pb were high (>100 µg/g) in bed sediment at some NROK* [Northern Rockies Intermontane Basins] *sites, Pb did not tend to accumulate in fish livers or fillets. This finding is particularly important because Pb has been identified as a pollutant of concern to humans and wildlife as a result of mining activities in this study area.* [25]

It is well-known that when fish (as well as mammals) ingest contaminated sediments or prey containing Pb, it does not build up in muscle tissue. Rather, most of the Pb body burden is found in bone, gills, liver, and kidney:

> *Lead can accumulate in bones, scales and skin (by sticking on to the skin surface). Lead can also be introduced from mucus and organs.* [26]

Because Pb is sequestered in fish tissues and organs that may only be eaten rarely (if ever), the agencies state that whole-fish samples are "not appropriate" for human health risk assessment:

> *However, because whole largescale sucker rather than the edible portion (fillets) were analyzed for suckers, the values reported are not appropriate for human health risk assessment.*

Furthermore, they assumed that children would not only eat whole fish, but that they would also consistently eat *only* the fish species with the highest whole-body Pb level—namely, largescale suckers. By their own admission, they did not think this a reasonable assumption: "However, it is highly unlikely that a child would consume only largescale suckers." [26]

Lacking an RfD, Pb-related risks cannot be evaluated in the same manner as other contaminants. Therefore, I chose to evaluate Pb from a toxicological standpoint. I have concluded that Pb-contaminated fish would not pose a health hazard even when the whole fish are eaten. This is because Pb is primarily bound to bones in fish and the chemical bond is so strong that even if a fish consumer ate the entire fish including bone, Pb would not be appreciable released from bone in the human gastrointestinal tract which is necessary for absorption into the body. That is, for Pb to be absorbed from the human gastrointestinal tract it must first be *desorbed* from the fish bone and because Pb is not desorbed from bone tissue (due to

the very strong chemical bond) it will not be significantly absorbed into the systemic blood circulation by the fish consumer.

If, for example, even when whole fish (bones and all) are used to make a stew or soup, Pb would not be significantly released into the water and most would still be bound to bone tissue. Furthermore, assuming a fish eater actually ate the bones it would not be in a *bioavailable* chemical form that could be absorbed from the microvilli lining the small intestine where most absorption occurs.

Simply put, Pb will not be bioavailable due to the tenacious stable chemical forces holding it in place in bone. Pb actually becomes part of the bone matrix. This is not just true in fish but when humans are exposed to Pb is stored for decades in bone tissue (which can be viewed as a protective physiological mechanism because only *free* unbound Pb can cross the blood brain barrier to cause brain damage and as long as it stored in bone it is not free).

When Pb is ingested by fish, it is sequestered into skeletal bone by forming a nearly unbreakable bond with the phosphate mineral apatite—which is the chemical structure of bones—to form pyromorphite; this stable crystalline mineral cannot be absorbed by the human digestive system (Freeman 2012). [27] For example, Miretzky et al. (2008) states that intentional or unintentional ingestion of pyromorphite does not pose a health threat because it cannot be made soluble in the physiological conditions of the gastrointestinal tract: [28]

> *Accidental pyromorphite ingestion does not yield bioavailable lead, because pyromorphite is insoluble in the intestinal tract.*

In fact, bone acts like a sponge to absorb Pb, and the resulting pyromorphite is so incredibly stable that it has been shown to be very effective biomaterial tool for remediating Pb-contaminated water at polluted sites: [27]

> *Adsorption onto biomaterials is one of the most promising processes for heavy metal remediation of contaminated water…The percent lead removed from the contaminated aqueous solution by each fish bone, carbonate and phosphate salt was calculated. Lead removal by the fish bone was greater than 99% for each type of fish bone used. The results further suggest that the fish bones removed slightly more lead than sodium carbonate and sodium phosphate. These results suggest that unmodified fish bone is a highly effective biomaterial for removing lead from contaminated water.*

Ground fish bones are even effective in sequestering Pb from contaminated soils: [27]

> *Now researchers are using fish bones and other phosphate-rich amendments to remediate lead in urban soils. "We have seen reduction in bioaccessibility in some lab samples up to fifty percent*

> *within just a few weeks of treatment," says Steve Calanog of the U.S. Environmental Protection Agency (EPA), who is overseeing an agency project using fish bones to clean up soils in the South Prescott neighborhood of Oakland, California.*

Pb stored in skeletal bone is essentially considered a protective toxicological mechanism in both fish and humans because it immobilizes Pb in the body in the solid bone matrix and prevents Pb-induced toxicity (Pb remains bound in bone for many decades). This is because only free or unbound Pb can reach the brain from the systemic blood circulation. This is a well-known fundamental principal in toxicology, which was even stated in the Health Consultation, but only in reference to human exposures:

> *Because of chemical similarities to calcium, lead can be stored in bone for many years. Even after exposure to environmental lead has been reduced, lead stored in bone can be released back into the blood where it can have harmful effects. Normally this release occurs relatively slowly.* [26]

In summary, the degree to which absorption of Pb into the human body after eating fish tissue contaminated with Pb depends on a variety of factors but the *sine qua non* is Pb bioavailability, as discussed previously. That is, in order for Pb to produce neurotoxic effects in a child, it must first be absorbed into the child's body from the gastrointestinal tract after a fish meal. Once the Pb-contaminated fish tissue reaches the stomach and small intestine, Pb must first be made *bioaccessible;* unless it is solubilized from fish tissue, it cannot be absorbed in the duodenum (the first part of the small intestine that is attached to the stomach). Bioaccessibility describes the process whereby Pb is first desorbed (the opposite of absorbed) from solid fish tissue matrixes like fish bone and other tissues in which it is made water-soluble and can be dissolved in the watery intestinal contents. Desorption from the solid state matrix is an absolute requirement for Pb because it must be soluble in the aqueous environment of the gastrointestinal tract (absorptive tissue lining the small intestine) in order for it to be transported through the cells lining the small intestine (gastrointestinal epithelium). Only the water-soluble fraction of Pb can pass through the cells lining the intestine, reach the intestinal blood capillaries, and enter the systemic blood circulation (via the hepatic portal vein). The portion that remains nonsoluble and bound to the solid fish tissue matrix cannot be absorbed, and that fraction will simply be eliminated in the feces. The percent bioavailability is one of the most important assumptions used in the U.S. EPA Pb models for calculating the BBL. The Health Consultation recommendation for eating whole fish contaminated with Pb is based on the assumption that 30% of the Pb in whole fish is bioavailable. Since Pb bound to fish bone represents the largest fraction in all fish organ systems and the Pb–bone fraction is not bioavailable, the bioavailability assumption of 30% Pb for children overestimates the BBL and risk to children.

1.11. Comparing the Maximum Allowable Fish Meal PCB Levels with Multiple Contaminants

In the previous sections, I evaluated the three fish contaminants separately, assuming only one contaminant was present in fish. Comparing those results shows that it is obvious that PCB is the greatest threat to Spokane fish consumers, and it is the most important contaminant that needs to be targeted by the City for remediation.

In this section I present the results in a somewhat different format. While the previous section allowed a side-by-side comparison of the three contaminants, it did not permit an evaluation of the health threat when just PCBs were removed from fish tissue. Therefore, it would be useful to know if fish consumers could eat more fish if Spokane's efforts succeeded in removing PCBs. For this analysis, I compared the maximum allowable fish meals based on all three contaminants (PCBs + PBDEs + Hg) being present (using 2012 data) to the scenario where Spokane was successful in removing PCBs, leaving only Hg and PBDEs in the fish tissues. This is the generally accepted toxicological practice of analyzing the magnitude of a single contaminant when investigating chemicals that all target the same body organ. In this analysis, the summed risks can be added since all three contaminants produce similar toxic effects in the central nervous system, causing neurological damage (particularly during development in young children and adolescents).

Ultimately, this analysis addresses the question, "Will remediating PCBs have a significant impact on fish consumption, even though fish will still be contaminated with other chemicals?" (i.e., is it worth it?). The answer is yes.

The calculated number of maximum fish meals will be significantly increased if PCBs are reduced even if PBDE and Hg are assumed to remain unchanged from 2012 levels. The table below in Exhibit 18 shows: 1) the number of fish meals that can be safely consumed for fish tissues contaminated with all three chemicals (PCBs, PBDE, and Hg); and 2) the maximum number of fish meals assuming PCBs are no longer in the fish. The first column shows the combined effect on fish meals resulting from the combined effect of just PBDE, and Hg this is juxtaposed with column 3 that shows that number meals is significantly decreased with all three contaminants (i.e., PCB + PBDE + Hg). The last column shows the increased number of fish meals in multiples when PCB is assumed to be absent from fish tissues. For example, the first row shows that when all contaminants are present only 1.4 fish meals can be eaten but

when PCB are removed, the number of meals is significantly increase to 4.4 meals, which is 3.1 times as many meals

Exhibit 18. Noncancer Health Effects, 2012 Data: Comparing the Maximum Allowable Fish Meals, With and Without PCB Contamination

River Section	Fish Species	Maximum Allowable Fish Meals- *PCBs Eliminated* ONLY=PBDE + Hg	Maximum Allowable Fish Meals With *All* Contaminants ALL=PCBs + PBDE + Hg	Differences In Multiples (x)
Spokane Arm	Largescale sucker (whole)	4.4	1.4	3.1
	Brown Trout (fillet)	6.9	3.5	2.0
	Rainbow Trout (fillet)	13.8	5.2	2.7
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	13.5	4.7	2.9
	Northern Pikeminnow (fillet)	5.2	3.3	1.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	5.1	1.4	3.7
	Mt whitefish (fillet)	4.2	1.7	2.4
	Northern Pikeminnow (fillet)	4.3	2.2	1.9
	Rainbow Trout (fillet)	10.5	3.7	2.9
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	9.0	2.7	3.4
	Mt whitefish (fillet)	1.7	0.9	1.9
	Rainbow Trout (fillet)	6.2	2.7	2.3
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	7.1	2.2	3.2
	Northern Pikeminnow (fillet)	4.2	3.1	1.4
	Rainbow Trout (fillet)	12.5	4.9	2.6
Average Difference				**2.5**

Notes: DOH 2012 Data McBride [10]
Assuming BW=60 kg; U.S. EPA RfD=0.0001 for Hg and PBDE; PCB RfD 0.00002
Orange Highlights = Average *de minimis* fish consumption rate 8 meals/month

This increase in the number of meals when PCB is reduced to zero has real-like consequences. That is, with PCB gone, fish consumers can enjoy the health-benefits of eating the *de minimis* recommended number of 1 fish meal per *week*. In fact, after PCBs are eliminated, the recommended number of fish can be eaten for all fish samples.

1.12. Rebuttal Response to Dr. Keenan's Critique of the Fish Consumption Rate

Dr. Keenan makes the following statements on page 6-3:

> *Dr. DeGrandchamp provides a discussion of risks associated with the ingestion of fish at a rate of 42 g/day (on average) and 90 g/day for higher-end consumers. As I discussed in Section 5.2, the 42 g/day fish ingestion rate presented by WDOH (2007), which was cited as based on studies conducted in the late 1990s that were not specifically designed to estimate fish consumption rates, is likely in error. A similar consumption rate was reported in ATSDR (2005). Even so, WDOH uses the 42 g/day value only in its screening assessment. Fish advisories are set assuming an 8-oz meal size, which equates to 32 g/day for one fish meal per week. The error associated with the 42 g/day consumption rate also puts into question the derivation and use of the higher end consumption rate of 90 g/day.*

Dr. Keenan is incorrect for several reasons. First, DOH does not use 42 g/day in its screening assessment. As I discussed previously, it uses 59.7 and 175 as fish ingestion rates to represent the average and upper-bound screening levels, as shown in Exhibit 19. (I have referred to these screening levels as *de minimis* fish tissue concentrations).

Exhibit 19. DOH Uses 59.7 and 175 g/day to Calculate Screening Levels

Fish Tissue Screening Levels (SL)

Noncancer endpoint

$$SL_{PCB\ Conc.} = \frac{RfD \times BW}{CR}$$

Cancer endpoint

$$SL_{PCB\ Conc.} = \frac{ARL \times BW}{CSF \times CR}$$

Analyte	RfD Noncancer (mg/kg-day)	CSL Cancer $(mg/kg\text{-}day)^{-1}$	Tissue SL (59.7 gm/day) ppb	Tissue SL (175 gm/day) ppb
PCBs	0.00002		23	8
PCBs		2	0.59	0.2
PBDEs	0.0001		100	34
Mercury	0.0001		100	34

Second, as I discussed previously, health groups and governmental agencies recommend that a healthy diet consist of 8–12 ounces of fish per week [29], which equals 32–48 g/day; this is considered the minimum daily fish ingestion rate. Exhibit 20 shows the recent recommendation by U.S. EPA–FDA for the number of fish meals pregnant women or women of childbearing age.

Exhibit 20. U.S. EPA–FDA Recommends 8–12 Ounces of Seafood per Week [3]

> Serving size is also consistent with the recommendation of 8-12 ounces of a variety of seafood per week from choices lower in methyl mercury found in the *Dietary Guidelines for Americans 2015* and USDA's. This is equivalent to 2-3 four-ounce servings per week.
>
> Weekly servings = 1, 2, or 3

Indeed, U.S. EPA–FDA also used a fish ingestion rate of 48 g/day (three 4-ounce servings) to calculate a screening level for eating Hg-contaminated fish. The agencies characterized this fish ingestion rate as being the healthiest, labeling it among "Best Choices" to encourage women to eat more fish. (See Exhibit 21.)

Exhibit 21. U.S. EPA–FDA Hg Fish Contamination Screening Levels Based on a Fish Ingestion Rate of 48 g/day Is among "Best Choices" [3]

Weekly fish servings	Screening value (µg/g)	Chart category
1	≤ 0.46	Good Choices
2	≤ 0.23	
3	≤ 0.15	Best Choices

Contrary to Dr. Keenan's opinion that a fish ingestion rate of 42 g/day may not be appropriate, it should be noted that when DOH set the assumed fish ingestion rate to 42 g/day, it essentially set a fish ingestion below even the minimum fish ingestion rate governmental health agencies recommend. [29]

Dr. Keenan also states on page 6-6:

> *Dr. DeGrandchamp also did not closely review WDOH's quoted risk results. These risk results were based on a consumption rate of 42 g/day, which, as stated earlier, is an error. The risk calculations should have been based on an 8-oz meal size, which equates to 32 g/day (at one fish meal per week). Use of this elevated fish consumption rate overestimates the potential risks by a factor of 1.3 (42/32).*

The document Dr. Keenan is referring is the *1997 Consumption Patterns of Anglers Who Frequently Fish Lake Roosevelt*, September 1997, DOH. [20] As I stated in my deposition, I reviewed this document to determine the source of the fish ingestion rate of 42 g/day. However, but since no raw data were presented, I evaluated the summary data in which DOH did present numerical estimates of the fish consumption rates. [20]

The above data within the report supports my opinion that a consumption rate of 42 grams per day is a reasonable fish consumption rate that will protect a large number of people eating PCB-contaminated fish. As I repeatedly stated in my deposition, the overarching goal of all health assessments intended to protect public health is to prevent the majority of the public—not just the average fish consumer—from eating an excessive amount of PCB-contaminated fish. As noted above, the fish consumption survey stated that the average fish consumption was 42 fish meals per year, which equates to an average (50th

percentile) daily fish consumption of 26 grams. However, the 90th percentile of those surveyed consumed 103.2 meals per year, or two meals per week, which is equivalent to 64 g/day. Thus, the fish ingestion rate of 42 g/day falls in the middle of these two consumption rates (i.e., 45 g/day), approximately corresponding to the 75th percentile. As I testified in my deposition, a 42 g/day ingestion rate was a reasonable assumption, as it protects about 75% of the population. Although it does not protect the entire population (with the target being 90%–95%), it is more protective than the 26 g/day average consumption rate, which only protects half the population. Therefore, while I did not cite this particular document in my expert report, the findings are not inconsistent with my opinion.

In addition, DOH stated that the primary target was license holders and fishing club members, which would have ignored those fishing without a license and those not belonging to a club:

> *A mail survey questionnaire sampled two fish-consuming populations based on a random sample of Spokane County fishing license holders (2000 sample population) and individuals from a particular Spokane area fishing club (180 sample population from The Walleye Club).* [20]

Part of that survey also included fishing consumption rates for ethnic groups like the Russian community. DOH concluded the rate for that group was 65 g/day: [20]

> *Key Russian Community Findings:*
>
> - *Harvest locations: Upriver Dam, the old Walk in the Wild Zoo, River Front Park, downtown Spokane area, T.J Meenach Bridge, Nine Mile Bridge, and Long Lake.*
> - *Fish harvested: rainbow trout, German (brown) trout, suckers, catfish, crayfish, pike minnow, smallmouth bass, and perch.*
> - *Fish consumption: about 4 pounds per month (about 65 g/day or 2.3 ounces of fish per day).*

1.13. Calculated Noncancer Hazard Quotient and Cancer Risk

Assuming higher ingestion rates – which are reflected by the above-discussed documents -- would significantly increase the risk under Keenan's analysis. In my above response to Dr. Keenan's critique that a fish ingestion rate of 42 g/day is not appropriate, I state that it is a reasonable assumption because it falls below even the *minimum* fish ingestion rates that are recommended by governmental health agencies. [29] In this section, I calculate the PCB noncancer hazard index and cancer risk (using the 2012 DOH fish tissue dataset) based on the fish ingestion rates that are the subject of this issue: 42 g/day. I

have also calculated the same hazards and risks assuming 64 g/day, since that was the 90th percentile for the fish ingestion rate.

I should also stress that the fish ingestion rate of 42 g/day is not germane to my opinion because using that assumption—which corresponds to about the 75th percentile (the 50th and 90th percentiles were 26 and 64 g/day, respectively) does not protect the entire population. The generally accepted practice in toxicology and risk assessment is to protect the entire population, which corresponds to the 95th–99th percentile; that would be greater than even the 90th percentile level of 64 g/day.

1.13.1. Equations for Calculating Daily PCB Dose from Eating PCB-Contaminated Fish

Noncarcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Dose}_{noncancer}\ (\text{mg/kg-day}) = [(C*CF1*IR*CF2*EF*ED)/(BW \times AT)]_{noncancer}$$

Carcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Dose}_{cancer}\ (\text{mg/kg-day}) = [(C*CF1*IR*CF2*EF*ED)/(BW \times AT)]_{cancer}$$

Noncancer Hazard Quotient

$$HQ = \text{Dose}_{noncancer} / RfD$$

Carcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Cancer Risk} = \text{Dose}_{cancer} * CSF$$

Exposure parameters and values used to calculate PCB dose are shown in Exhibit 22.

Exhibit 22. Exposure Assumptions for Calculating the HQ and Cancer Risk

Parameter	Value	Unit	Comments
Concentration (C)	Variable	ug/kg	Mean Fish Tissue Concentration
Conversion Factor (CF_1)	0.001	mg/ug	Converts contaminant concentration from micrograms (ug) to milligrams (mg)
Ingestion Rate (IR)	42 and 64 g/day	g/kg/day	Average recreational anglers (42 g/day)
Conversion Factor2 (CF_1)	0.001	mg/ug	Converts contaminant concentration from micrograms (ug) to milligrams (mg)

Conversion Factor2 (CF_2)	0.001	kg/g	Converts mass of fish from grams (g) to kilograms (kg)
Exposure Frequency (EF)	365	days/year	Assumes daily exposure consistent with units of ingestion rate given in g/day
Exposure Duration (ED)	30 (adult) 5 (child)	years	Number of years eating fish
Averaging Time $_{noncancer}$ (AT)	10950	days	30 years
Averaging Time $_{cancer}$ (AT)	25550	days	70 years
Oral Reference Dose (RfD)	2E-5	mg/kg-day	Source: USEPA, IRIS (2019)
Cancer Slope Factor (CSF)	2	mg/kg-day-1	Source: USEPA, IRIS (2019)

Exhibit 23 presents the hazard quotients for PCB-contaminated fish using the 2012 DOH data and assuming a fish ingestion rate of 42 g/day for both the 50% PCB concentration and the full PCB concentration. As this table shows, more than 11 of the fish samples (11/15; 73%) exceeded the safe daily intake (based on the RfD), which is HQ = 1.0. All HQ results exceeded 1.0 for the fish samples that were not adjusted to account for a reduction in PCB concentration resulting from recommended fish preparation.

Exhibit 23. Calculated Hazard Quotient (HQ) for 2012 Fish Tissue Data Assuming a Fish Ingestion Rate of 42 g/day

River Section	Fish Species	PCB Concentration 50% Reduction	Hazard Quotient 50% Reduction	PCB Concentration No Reduction	Hazard Quotient No Reduction
Spokane Arm	Largescale sucker (whole)	113.8	3.4	227.6	6.8
	Brown Trout (fillet)	33.3	1.0	66.6	2.0
	Rainbow Trout (fillet)	28.8	0.9	57.6	1.7
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	1.0	66	2.0
	Northern Pikeminnow (fillet)	25.9	0.8	51.8	1.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	3.8	252	7.6
	Mt whitefish (fillet)	81.6	2.4	163.2	4.9
	Northern Pikeminnow (fillet)	53	1.6	106	3.2
	Rainbow Trout (fillet)	43	1.3	86	2.6

RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	1.9	126	3.8
	Mt whitefish (fillet)	125	3.8	250	7.5
	Rainbow Trout (fillet)	49.3	1.5	98.6	3.0
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	2.3	150.2	4.5
	Northern Pikeminnow (fillet)	21.6	0.6	43.2	1.3
	Rainbow Trout (fillet)	29.9	0.9	59.8	1.8

Exhibit 24 shows the hazard quotient for PCB-contaminated fish for the 2012 DOH data assuming a fish ingestion rate of 64 g/day for both the 50% PCB concentration and the full PCB concentration. As this table shows, all HQ results exceeded 1.0.

Exhibit 24. Calculated Hazard Quotient (HQ) for 2012 Fish Tissue Data Assuming a Fish Ingestion Rate of 64 g/day

River Section	Fish Species	PCB Concentration 50% Reduction	Hazard Quotient 50% Reduction	PCB Concentration No Reduction	Hazard Quotient No Reduction
Spokane Arm	Largescale sucker (whole)	113.8	5.2	227.6	10.4
	Brown Trout (fillet)	33.3	1.5	66.6	3.0
	Rainbow Trout (fillet)	28.8	1.3	57.6	2.6
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	1.5	66	3.0
	Northern Pikeminnow (fillet)	25.9	1.2	51.8	2.4
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	5.8	252	11.5
	Mt whitefish (fillet)	81.6	3.7	163.2	7.5
	Northern Pikeminnow (fillet)	53	2.4	106	4.8
	Rainbow Trout (fillet)	43	2.0	86	3.9
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	2.9	126	5.8
	Mt whitefish (fillet)	125	5.7	250	11.4

	Rainbow Trout (fillet)	49.3	2.3	98.6	4.5
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	3.4	150.2	6.9
	Northern Pikeminnow (fillet)	21.6	1.0	43.2	2.0
	Rainbow Trout (fillet)	29.9	1.4	59.8	2.7

Exhibit 25 shows the cancer risk for PCB-contaminated fish based on the 2012 DOH data and assuming a fish ingestion rate of 42 g/day. All cancer risks exceed *de minimis* cancer risks, as well as the 1E-4 cancer risk threshold Dr. Keenan set as an acceptable risk.

Exhibit 25. Calculated Cancer Risk for 2012 Fish Tissue Data Assuming a Fish Ingestion Rate of 42 g/day

River Section	Fish Species	PCB Concentration 50% Reduction	Cancer Risk 50% Reduction	PCB Concentration No Reduction	Cancer Risk No Reduction
Spokane Arm	Largescale sucker (whole)	113.8	1.4E-04	227.6	2.7E-04
	Brown Trout (fillet)	33.3	4.0E-05	66.6	8.0E-05
	Rainbow Trout (fillet)	28.8	3.5E-05	57.6	6.9E-05
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	4.0E-05	66	7.9E-05
	Northern Pikeminnow (fillet)	25.9	3.1E-05	51.8	6.2E-05
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	1.5E-04	252	3.0E-04
	Mt whitefish (fillet)	81.6	9.8E-05	163.2	2.0E-04
	Northern Pikeminnow (fillet)	53	6.4E-05	106	1.3E-04
	Rainbow Trout (fillet)	43	5.2E-05	86	1.0E-04
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	7.6E-05	126	1.5E-04
	Mt whitefish (fillet)	125	1.5E-04	250	3.0E-04
	Rainbow Trout (fillet)	49.3	5.9E-05	98.6	1.2E-04
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	9.0E-05	150.2	1.8E-04
	Northern Pikeminnow (fillet)	21.6	2.6E-05	43.2	5.2E-05
	Rainbow Trout (fillet)	29.9	3.6E-05	59.8	7.2E-05

Exhibit 26 shows the cancer risk for PCB-contaminated fish based on the 2012 DOH data and assuming a fish ingestion rate of 64 g/day. As shown for the above calculations, all cancer risks exceed *de minimis* cancer risks, as well as the 1E-4 cancer risk threshold Dr. Keenan set as an acceptable risk.

Exhibit 26. Calculated Cancer Risk for 2012 Fish Tissue Data Assuming a Fish Ingestion Rate of 64 g/day

River Section	Fish Species	PCB Concentration 50% Reduction	Cancer Risk	PCB Concentration No Reduction	Cancer Risk
Spokane Arm	Largescale sucker (whole)	113.8	2.1E-04	227.6	4.2E-04
	Brown Trout (fillet)	33.3	6.1E-05	66.6	1.2E-04
	Rainbow Trout (fillet)	28.8	5.3E-05	57.6	1.1E-04
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	6.0E-05	66	1.2E-04
	Northern Pikeminnow (fillet)	25.9	4.7E-05	51.8	9.5E-05
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	2.3E-04	252	4.6E-04
	Mt whitefish (fillet)	81.6	1.5E-04	163.2	3.0E-04
	Northern Pikeminnow (fillet)	53	9.7E-05	106	1.9E-04
	Rainbow Trout (fillet)	43	7.9E-05	86	1.6E-04
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	1.2E-04	126	2.3E-04
	Mt whitefish (fillet)	125	2.3E-04	250	4.6E-04
	Rainbow Trout (fillet)	49.3	9.0E-05	98.6	1.8E-04
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	1.4E-04	150.2	2.7E-04
	Northern Pikeminnow (fillet)	21.6	3.9E-05	43.2	7.9E-05
	Rainbow Trout (fillet)	29.9	5.5E-05	59.8	1.1E-04

2. FISH CONSUMPTION RISKS AS DEFINED BY LAW ARE BASED ON THE *DE MINIMIS* CANCER RISK LEVEL 1E-6

Rebuttal to Dr. Keenan's statement that a cancer risk level of 1E-6 to 1E-4 is acceptable because it falls within EPA's acceptable risk range.

While I do agree with Dr. Keenan's statement, and he has correctly cited the U.S. EPA risk management framework (which is explained in the "Don Clay memo") [30]—-which I have relied on for most of my 300 HHRAs—it is not applicable to this case. This is not an U.S. EPA-led site; there is no U.S. EPA remedy to be evaluated, so Dr. Keenan is citing a risk management framework that is not germane. As I discussed in great detail in Volume 3 of my expert report, DOH is the lead agency responsible for protecting the health of Spokane fish consumers. Furthermore, and perhaps more importantly, Dr. Keenan is ignoring the Washington State law that governs the acceptable risk for fish consumption. That law is the National Toxics Rule (NTR), which is overseen by Ecology: [31]

> *Washington State's water quality standards for toxic substances (WAC 173-201A-040[5]) define human health-based water quality criteria by referencing 40 CFR 131.36, also known as the National Toxics Rule (NTR).* [31]

The NTR specifically considers fish consumption of contaminated fish to make a determination on whether Washington water bodies are meeting health-based standards:

> *The NTR criteria were issued by EPA to Washington State in 1992. These criteria are designed to minimize the risk of adverse effects occurring to humans from chronic (lifetime) exposure to toxic substances through the ingestion of drinking water and contaminated fish and shellfish obtained from surface waters. The NTR criteria are regulatory values used by Ecology for a number of different purposes, including permitting wastewater discharges and assessing when waterbodies are adversely impacted by contaminants.* [31]

Most importantly, the NTR criteria are specifically based on a 1E-6 cancer risk level:

> *The NTR criteria values are based on a daily fish consumption rate of 6.5 grams/day and a risk level of 10-6…A risk level is an estimate of the number of cancer cases that could be caused by exposure to a specific contaminant. At a risk level of 10-6, one person in a million would be expected to contract cancer due to long-term exposure to a specific contaminant.* [31]

Dr. Keenan has ignored the NTR criteria. In my experience, risk-based levels as defined by U.S. EPA and state laws trump or supersede the results of site-specific risk assessments (for example, when groundwater

risks are compared to chemical-specific Maximum Contaminant Levels [MCLs: defined in the Clean Drinking Water Act], MCLs are always used as the groundwater risk standard). That is, environmental laws or policies, which are referred to by U.S. EPA as Applicable or Relevant and Appropriate Requirements (ARARs) are usually given deference and weighted more heavily than the results of a risk assessment. Indeed, the U.S. EPA risk management framework Dr. Keenan cites (the Don Clay memo [30]) was specifically developed for Superfund sites—not fish consumptions advisories—states that ARARS need to be considered: [30]

> *Specifically, the following points are made in the memorandum:*
>
> *Where the cumulative carcinogenic site risk to an individual based on reasonable maximum exposure for both current and future land use is less than 10(-4) and the non-carcinogenic hazard quotient is less than 1, action generally is not warranted unless there are adverse environmental impacts. However, if MCLs or non-zero MCLGs are exceeded, action generally is warranted.* [30]

Indeed, ARARS are one of the two threshold criteria in the National Contingency Plan (NPL). [32]

As DOE states, exceedances of the risk-based values established in the NTR may trigger state enforcement action under the Clean Water Act (which is a Statute):

> *The NTR criteria are thresholds that, when exceeded, may lead to regulatory action. When water quality criteria are exceeded, the federal Clean Water Act requires that the waterbody be put on a list and that a water cleanup plan be developed for the pollutant causing the problem. This list is known as the 303(d) list, and the water cleanup plan results from a Total Maximum Daily Load (TMDL) study and public involvement process. Ecology uses the TMDL program to control sources of the particular pollutant in order to bring the waterbody back into compliance with the water quality standards.*

Exhibit 27 lists the NTR screening fish tissue concentrations. Based on the 2012 Spokane fish sampling dataset, all fish samples exceed the NTR levels, even though these fish tissue PCB concentrations are based on a daily fish consumption rate of 6.5 grams/day.

Exhibit 27. National Toxics Rule Criteria, National Recommended Water Quality Criteria, and EPA Screening Values for the Protection of Human Health for Contaminants Detected in Fish Tissue, WSTMP 2004–2005 [21]

Analyte (ppb ww)[1]	National Toxics Rule	National Recommended Water Quality Criteria [2]	EPA Screening Values			
			Subsistence Fishers		Recreational Fishers	
			Noncancer	Cancer	Noncancer	Cancer
Mercury	825	300	49	-	400	-
Total PCBs [3]	**5.3**	**2.0**	**9.83**	**2.45**	**80**	**20**
2,3,7,8-TCDD [4]	0.07	-	-	-	-	-
2,3,7,8-TCDD TEQ 4, 5	-	0.026	-	0.0315	-	0.256
4,4'-DDD	45	17	-	-	-	-
4,4'-DDE	32	12	-	-	-	-
4,4'-DDT	32	12	-	-	-	-
Total DDT [6]	-	-	245	14.4	2000	117
Chlordane [7]	8.3	11	245	14.0	2000	114
Aldrin	0.65	0.23	-	-	-	-
Alpha-BHC	1.7	0.64	-	-	-	-
Beta-BHC	6.0	2.2	-	-	-	-
Chlorpyriphos	-	-	147	-	1200	-
Chlorthal-Dimethyl (Dacthal)	-	-	-	-	-	-
Dieldrin	0.65	0.25	24	0.307	200	2.5
Endosulfan Sulfate	540	24000	-	-	-	-
Endrin	3200	230	147		1200	
Heptachlor Epoxide	1.2	0.44	6.39	0.54	52	4.39
Hexachlorobenzene	6.7	2.5	393	3.07	3200	25.0
gamma-BHC (Lindane)	8.2	230	147	3.8	1200	30.7
Methoxychlor	-	-	-	-	-	-
Mirex	-	-	98	-	800	-
Pentachloroanisole	-	-	-	-	-	-
Toxaphene	9.8	3.7	122	4.46	1000	36.3
PBDEs	-	-	-	-	-	-

These NTR-derived PCB concentrations should not be considered conservative because a fish consumption rate of 6.5 g/day is far less than even the minimum fish consumption rate recommended by governmental health agencies of 32–48 g/day (8–12 ounces/week).[29] Moreover, DOH uses daily fish consumption rates of 59.7 and 175 g/day, which correspond to fish tissue PCB concentrations of 0.59 and 0.2 ppb, respectively (which are even less than the NTR PCB concentrations shown in Exhibit 27),which correspond to the *de minimis* cancer threshold.

DOE stresses that while it coordinates with DOH, it is DOH that is mandated with protecting public health: [21]

> *Most fish tissue contaminant data from Washington fish, regardless of who conducted the study, make their way to DOH for evaluation regarding the safety of consuming contaminated fish. The following is an overview of how Ecology and DOH evaluate fish tissue data to meet different needs.*

> *Ecology's role is to determine whether water quality standards are met and to begin the process to correct problems where standards are not met. DOH and local health departments are responsible for developing fish consumption advisories in Washington. There is some overlap in these evaluations because the water quality standards that fish tissue data are compared to were developed for the protection of human health.*
>
> *Washington's water quality standards criteria for toxic contaminants were issued to the state in EPA's 1992 National Toxics Rule (NTR) (40CFR131.36). The human health-based NTR criteria are designed to minimize the risk of effects occurring to humans from chronic (lifetime) exposure to substances through the ingestion of drinking water and consumption of fish obtained from surface waters. The NTR criteria, if met, will generally ensure that public health concerns do not arise, and that fish advisories are not needed.*[21]

Exhibit 28 shows the *de minimus* fish tissue PCB concentrations DOH has derived for both cancer and noncancer health effects. The differences between *de minimis* values is due to the slightly different methodologies used by DOE and DOH. What is notable, however, is that neither DOH nor DOE apply the probabilistic HHRA methodology Dr. Keenan uses.

Exhibit 28. DOH *De Minimis* Fish Tissue PCB Concentrations [10]

Fish Tissue Screening Levels (SL)

Noncancer endpoint $SL_{PCB\ Conc.} = \frac{RfD \times BW}{CR}$

Cancer endpoint $SL_{PCB\ Conc.} = \frac{ARL \times BW}{CSF \times CR}$

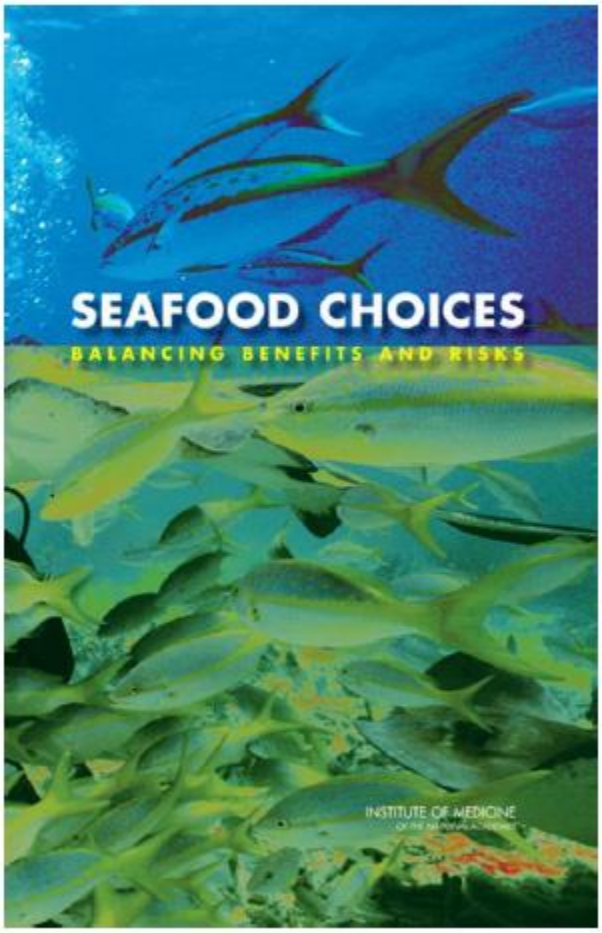
Analyte	RfD Noncancer (mg/kg-day)	CSL Cancer $(mg/kg\text{-}day)^{-1}$	Tissue SL (59.7 gm/day) ppb	Tissue SL (175 gm/day) ppb
PCBs	0.00002		23	8
PCBs		2	0.59	0.2
PBDEs	0.0001		100	34
Mercury	0.0001		100	34

Considering the above information begs the question of why DOH does not default to the PCB fish tissue levels corresponding to either the NTR or DOH-derived PCB contaminant levels that would protect Spokane fish consumers from developing cancer? The answer is that DOH has adopted a public health approach that balances the benefits and risks of eating PCB-contaminated fish. As I discussed previously, although a diet rich in fish tissue is necessary to maintain optimal health, this comes at a cost of consuming toxic amounts of PCBs that cause noncancer and cancer health effects. Therefore, to minimize the PCB-toxicity and maximize the health benefits, DOH has little choice but to ignore the PCB cancer

risks. DOH has opted instead to focus on the health benefits and calculate fish consumption rates only on the noncancer effects. To do otherwise would effectively place a total ban on eating Spokane PCB-contaminated fish. While this is reasonable and widely accepted public health policy, it remains a fact that the PCB-contaminated fish are well above the *de minimis cancer* risk level.

DOH's health policy on dealing with PCB-contaminated fish to develop its fish consumption advisories follows the recommendations of the NASIOM guideline in its thoughtful and well-reasoned book, *NAS Seafood Choices: Balancing Benefits and Risks* (2007). [29] (See Exhibit 29.)

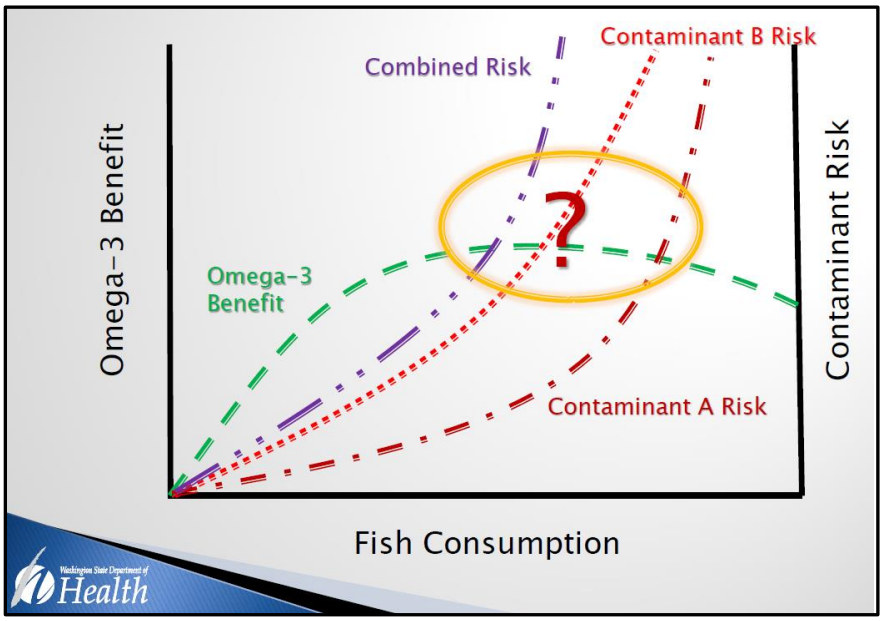
Exhibit 29. NAS Seafood Choices: Balancing Benefits and Risks (2007)



Although the NAS book provides an excellent overview of the toxicity of contaminants in fish and the health benefits of eating fish, it is largely qualitative, and its recommendations are fairly general. DOH has taken some of that information to make it somewhat quantitative, as shown in the schematic in

Exhibit 30. This graph shows a fish consumption dose-response curve with both the omega-3 benefits and contaminant health risks on the y-axis (on either side of the graph). Although the omega-3 benefits increase with increasing fish consumption, at a point there is no additional health benefit (and the omega-3 curve reaches a maximum level and levels off; this would be the point of maximum benefit). At the same time, with increasing fish consumption, the contaminant toxicity increases, exceeding the safe daily intake being. The maximum health–benefit *point* occurs when the omega 3-curve intersects with the toxic contaminant curves (there are two contaminants shown, and they have different toxicities). Although this schematic illustrates the concept, the single health–benefit point is difficult to actually quantify. However, the one fact that is obvious from this graph is that *if* DOH considered cancer as the toxic endpoint (which they do not), Spokane fish consumers would get no benefit from the health effects of a fish-rich diet because the recommended number of fish meals that would be safe to eat at *de minimis* cancer risk levels (based on the 2012 fish data) would be reduced by orders of magnitude.

Exhibit 30. DOH Graph Illustrating the Health–Benefit Analysis that Underlies Its Fish Consumption Advisories



This graph also shows that it is urgent that PCB levels in fish be reduced so that Spokane fish consumers can take full benefit of the nutritional advantages of an inexpensive source of fish oil containing omega 3. With every new medical study, more information shows just how beneficial fish are in preventing or

treating cardiovascular disease. For example, very recently (last week; December 13, 2019) FDA approved a new fish oil drug to reduce the likelihood of heart attacks and stroke: [33]

> *The U.S. Food and Drug Administration on Friday expanded the approved use of a fish-oil-derived drug to reduce the likelihood of heart attacks and strokes in high-risk patients.*
>
> *The drug, Vascepa from Amarin Corp. PLC, now becomes a new tool for reducing the risk of heart attacks, strokes and deaths in millions of heart-disease or diabetes patients with elevated triglycerides while opening up a multibillion-dollar commercial opportunity for its maker. The expanded label could mean Vascepa sales surpass $3 billion, analysts say. Last year's sales approached $230 million.*
>
> *Vascepa was approved in the U.S. in 2012 to treat adults with severe hypertriglyceridemia, or very high levels of triglycerides, which are fats that circulate in the blood. Since then, Amarin has been exploring whether the drug's effect goes further by reducing the risk of heart disease.* [33]

As I have stated previously, the current levels of PCBs in Spokane fish prevent fish consumers from enjoying the benefit of a low-cost source of fish oil, and the City of Spokane's efforts to reduce PCB loading will have the greatest effect on reducing not only the toxicity of PCBs but increasing the overall well-established health benefits of a diet rich in fish tissue, particularly fish oil containing omega-3, heart-healthy fatty acids.

3. BACTERIA AND OTHER CONTAMINANTS DO NOT INTERFERE WITH FISH CONSUMPTION

This sections addresses the various references in Defendants' expert reports (Herman and Desvousges) to bacteria and other contaminants that do not affect fish consumption. There is no fish consumption advisory or other limit on the consumption of fish based on bacteria, algae blooms, phosphorous, dissolved oxygen, or various other contaminants cited in their reports (other than mercury, lead, PCBs, and PBDEs).

For the remainder of this section, I discuss contaminants related to sewage. In brief, my opinion is that sewage directly released into the Spokane River would have no impact on the health risks associated with eating PCB-contaminated fish.

Bacterial infections, illness, and disease associated with human exposure to pathogenic strains is a topic of interest to me and an area in which I have considerable expertise. I teach a graduate-level course in Environmental Epidemiology in which I lecture on the contagious transmission, vectors, and the damage

caused by toxins released by pathogenic bacteria. I cover many *waterborne* strains, including those that cause cholera (*Vibrio cholerae*; serogroup O1 or O139) and hemolytic uremic syndrome (HUS; *Escherichia coli*; the *E. Coli* H:O157 strain).

There has been no laboratory-confirmed case of cholera in the United States for many years; while sewage may be released into the Spokane River, cholera is of no concern. While there are many strains of *E. coli* (one of the most bountiful bacteria in our gastrointestinal microbiome), most are not pathogenic; some are even beneficial and produce vitamin K (which humans cannot synthesize and are necessary for blood clotting). However, some, such as *E. Coli* H:O157, can cause morbidity and death (particularly in children who develop HUS, which has a high mortality rate). Fortunately for humans, we do not harbor this strain but can be exposed via contact with animals. The major source of pathogenic *E. coli* is farm animals like cows, sheep, pigs, etc. What makes this strain so dangerous is that the infected animals are asymptomatic, so ranchers and farmers are never aware of this potentially deadly strain infecting their herd.

Bacteria are not transported through the fish skin so they would not contaminate the edible parts of the fish. Any pathogenic bacterial contamination of Spokane water would enter and be isolated in the fish gastrointestinal tract which is most often removed during the fish preparations stage, even when the fish is eaten whole.

It should also be noted that sewage has been shown to be effective in degrading PCBs. [34][35][36] For example, Mathews and Sithebe concluded: [22]

> *Pseudomonas aeruginosa, isolated from wastewater in the Notwane Sewage Treatment Plant was successfully used in biodegradation of recalcitrant polychlorinated biphenyls (PCBs). This having been successfully employed at the micro level, and further tests can be carried out to validate the results obtained in this study. With this recommendation in place, it is ideal to say that employing bacteria in the biodegradation processes of recalcitrant PCBs will be highly cost effective as it is a biotechnological process.* [34]

In a study of PCBs in the Sheboygan Harbor, Michigan, Sonzogni states: [37]

> *Mono, di, and trihalobenzoates have been found to be completely mineralized to carbon dioxide and methane using bacteria from lake sediments and sewage sludge as well as enriched cultures grown on 3-chlorobenzoate (Suflita et al., 1982; Horowitz et al., 1983).*

In summary, the bacteria from human waste in sewage does not create a health risk when eating fish from the Spokane River.

4. DR. KEENAN STATES THAT I MISREPRESENTED EXPOSURES TO MINORITY POPULATIONS

Dr. Keenan did not focus on minorities, ethnic groups, or those who fish out of need to supplement their diets. Due to concern about authorities inquiring about fishing, fish preparation, and consumption, many minorities do not participate in fishing surveys. This includes ethnic minorities and those who fish out of poverty. In some cases, there is a language barrier; in other cases, there is mistrust of authority figures. Whatever the reason, this group collectively is largely underrepresented in fish consumption surveys. This is supported by survey results collected by DOH, DOE and the SRHD, Assessment/Epidemiology Center. [23]

SRHD states in its 1998 report:

> ***Barriers***
>
> *Both cultural and language barriers inhibited the free exchange of information within both of the above focus groups. Cultural barriers included the inherent mistrust of public officials and the concept of focus groups as a method of research which would protect their anonymity. This latter cultural barrier was more apparent among the Russian community, however, the event took place in a naturally occurring and spontaneous setting in their church.*
>
> *Representatives from both communities expressed concerns over the purpose of our questions. They wanted reassurance we were not inspectors or regulators there to get information that could*
> *incriminate them for fishing without a license. The Russian group seemed particularly concerned with the amount of information the facilitators had regarding the sources of metal contamination and the safety of the fish consumed from the Spokane River.* [20]

The report emphasized that language barriers are often difficult to surmount:

> *The facilitators felt that the language barriers also contributed to their inability to fully explain the purpose and the process of the study. This may, in fact, be responsible for the low participation from the Laotian community and the low response rate from the translated surveys.* [20]

It is also important to stress that some who fish the Spokane River do so for a good portion of their lives:

> *The respondents who fish the Spokane River reported the number of years they have fished the river. The range was 0 to 80 years. The mean for the number of reported years the river was fished by any one respondent is 13.51 years.* [20]

The fish survey also showed that it is not the affluent who fish, but rather those with modest incomes. However, those in poverty or with low incomes may not have contributed to the survey data. The income breakdown for those who participated were reported in the following statements.

> ***Survey Demographics***
> *The most commonly reported income was $40,000 to $59,999 (60 respondents, 24.3%). Forty respondents reported their income as $60,000 to $79,999 (16.2%), followed by 25 respondents (12.0%) reporting their income as $30,000 to $39,999.* [20]

Children are also likely underreported, and Dr. Keenan did not focus on this group in great detail. The survey reported that about 44% of the respondents had children, who likely shared in family fish meals.

> *Almost half of the respondents reported children in their household (44.1%, 109 households). The number of households with children who eat fish is 85. Adults eat fish in 232 of the respondents' households.* [20]

It is also important to note that the Russian community reported eating a variety of fish, not just sport fish. These included bottom-feeding fish that have the highest PCB concentrations. Furthermore, they are not sport fishermen and do not catch and release their fish. They eat all of their catch or give it away to someone else who will eat it.

> *The locations attendees reported fishing were, the old Walk in the Wild Zoo, Upriver Dam, River Front Park, downtown area, T.J. Meenach Bridge, Nine Mile Bridge, and Long Lake. Attendees reported catching rainbow trout, German (brown) trout, suckers, catfish, crayfish, pike minnow, smallmouth bass, and perch from the river.*
>
> *When asked what they do with the fish they catch (eat it, give it away, or release it) overwhelmingly they responded they either eat it or give it away. They only lose the fish "if it jumps off the hook or it is too small".* [20]

Most importantly, the Russian Community does not follow the fish preparation advice from DOH. This has a significant impact on their health, as I previously discussed. If they eat the fish without cooking, they will exceed the fish consumption advisories by 2-fold for PCBs because the number of fish meals per month is based on a 50% reduction in PCB fish tissue levels. None of the reported fish preparation methods follow DOH guidance.

> *Respondents identified five ways in which they prepare the fish from the Spokane River to eat: cutlets (ground fish-cakes), fried, dried, fish soup, and pickled (herring). The cutlets are prepared by grinding the fish after removal of head and spine; the tiny bones are included in the cutlets. It was reported that a common method to prepare sucker fish to eat was to make cutlets with them. To dry the fish, respondents report, the fish are salted while raw and then dried; they are never cooked. The whole fish is used when it is dried excluding the intestines and the head. Fish soup is prepared in different ways. Some people use the head others do not. The herring is pickled fish*

that is stored in a jar and does include bones. [18]

The survey results for the Laotian community put a fine point on my opinion that ethnic groups typically do not care to become actively involved in fish surveys (which has been my experience). Only six out of an estimated 200 in the community participated and provided information for the survey.

> *A total of six people participated in answering questions and entering into a discussion about the Spokane River and their fishing practices. General demographic information was uncovered at two meetings. The average family size for the Laotian community is four. It was estimated that the number of people in the Laotian community in Spokane County was approximately 200.* [18]

Like the Russian community, members of the Laotian community eat what they catch and also eat bottom-feeding fish like catfish (discussed in Volume 3 of my expert report).

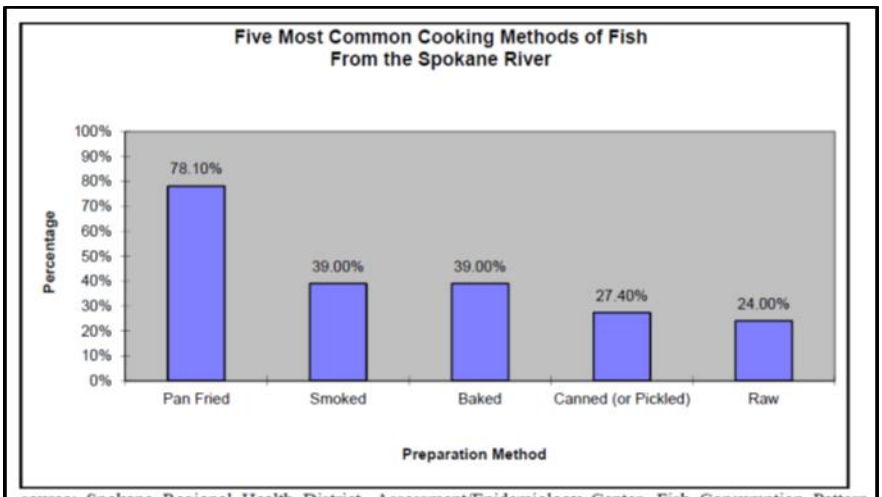
> *The fish that are caught from the river are generally used for consumption; they do not give them away. Thea attendees mentioned eating and knew of others to eat catfish, rainbow trout, perch, bass, walleye, and crawdads.* [18]

They also described fish preparation methods that are inconsistent with the DOH-recommended practices since it appears that they do not cook the fish to decrease the fish oil. Rather, methods like barbecuing and broiling tend to retain the oil and may be why they prepare the fish in this manner.

> *The identified methods of preparing the fish to eat included frying, smoking, barbecuing, broiling, and in stews. They reported that the fish are always cleaned and gutted, they do not eat the bones, and always cut off the heads before preparing the fish to eat.* [18]

In fact, the number of fish respondents who do not pan fry their fish meal is considerable, showing a large portion of those surveyed may be exceeding the safe daily intake (RfD) of PCBs. (See Exhibit 31.)

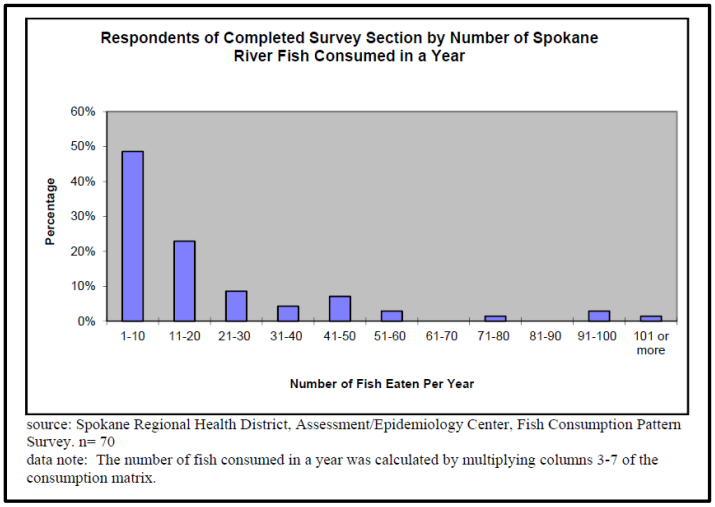
Exhibit 31. Many Fish Consumers Do Not Pan Fry Their Fish to Remove the PCB-Containing Fish Oil [18]



source: Spokane Regional Health District, Assessment/Epidemiology Center, Fish Consumption Pattern Survey, n= 247
data note: Survey Question 5 "How do you usually prepare fish from the Spokane River?"

As seen in Exhibit 32, approximately 5% of fish consumers (among those who participated in the survey) eat eight meals or more a month (96 meals per year), which is *not* safe for any fish species, according to the DOH Fish Consumption Advisories. It should also be noted that this survey was conducted in 1998, when the PCB levels were considerably higher than they are currently (2012); because PCBs are eliminated so slowly from the body, those consumers likely have significant PCB body-burden levels even today.

Exhibit 32. About 5% of Fish Consumers Reported Eating about eight Meals per Month [18]



source: Spokane Regional Health District, Assessment/Epidemiology Center, Fish Consumption Pattern Survey, n= 70
data note: The number of fish consumed in a year was calculated by multiplying columns 3-7 of the consumption matrix.

Dr. Keenan relies heavily on fish consumption surveys but he does not acknowledge the significant uncertainty in the results and biases are very difficult to overcome. He seems to consider survey information a very accurate snapshot of real life. As was indicated in the 1998, weaknesses in fish consumption surveys [23] include those listed below and in Exhibit 33 and Exhibit 34. Many of the weaknesses of all of these fish survey methods will likely underrepresent ethnic groups

In addition to the 1998 SRHD report, a more recent 2013 DOH fish survey provides a very detailed analysis of Washington fish consumers and includes a long list of some of the uncertainties and bias in fish consumption surveys. [23]

For example, DOH notes that creel surveys only provide information on fishermen who were actively fishing that day. As shown in Exhibit 33, there are many weakness that could bias the study and under report those in poverty or in ethnic minorities. [23] Those include the following:

- Language barriers may exist between participants and interviewers;
- Survey results cannot be generalized to the entire population;
- May miss anglers if not all fishing locations and times are surveyed;
- May under- or overestimate yearly consumption if survey is not conducted throughout the year; and
- Anglers may not be as receptive to engaging in interviews as preselected personal interview survey interviewees.

Exhibit 33. Strengths and Weaknesses of Creel Surveys [23]

Table 9. Strengths and Weaknesses of Creel Surveys

Strengths	Weaknesses
* Can assess site-specific consumption rates. * Can target specific at-risk populations who fish at contaminated sites. * The interviewer can observe the participant's fishing behaviors and catch as well as the condition of the interview site. * Recall bias is minimized by using visual aids and by having the interviewer refer to the fish caught around the time of the interview as a reference. * Results can be verified by looking at the daily catch of the participant. * Response rate is high. * More information can be gained by using visual aids and probing questions. * Creel surveys are routinely done for fishery management purposes; adding fish consumption questions to the surveys can be done with little added cost.	* Only a limited number and types of questions are used to minimize survey time. * Language barriers may exist between participants and interviewers. * Surveys require well-trained staff that must be monitored for quality control. * If interviews are occurring at fishing sites, answers about consumption are hypothetical because the fish have not yet been consumed. * Participants who fish more frequently are more likely to be interviewed than those who fish less frequently. [a] * Survey results cannot be generalized to the entire population. * May miss anglers if not all fishing locations and times are surveyed. * May under- or overestimate yearly consumption if survey is not conducted throughout the year. * Pilot testing for a target population is not as effective as is the case with personal interview surveys. * Anglers may not be as receptive to engaging in interviews as preselected personal interview survey interviewees. * Fears of contact with government officials may inhibit responses of minority groups. * Anglers in the field may not be as inclined or ready to respond as individuals that have been contacted and readied to participate in a personal interview survey. * Visual aids for unique seafood preparations are difficult to develop without knowledge of the target population. * If the water body is known to have chemical contamination, rates may be impacted by a suppression effect (i.e., the suppression of the harvest and consumption of fish), and hence may not result in protective risk estimates or cleanup levels. * It may difficult to know who actually consumes the fish.

a. Moya et al., 2008.

As shown in Exhibit 34, mail recall surveys also have many weaknesses and do not contain sufficient representation by minorities or those in poverty. [23] They include the following:

- Cannot reach people without mailing addresses;
- Higher number of inaccurate and incomplete responses; and
- May miss respondents who are illiterate, or have difficulty in understanding questions, or who cannot read the language.

Exhibit 34. Strengths and Weaknesses of Recall Mail Surveys [23]

Table 13. Strengths and Weaknesses of Recall Mail Surveys

Strengths	Weaknesses
* Can assess region-specific consumption rates. * Can target and identify specific subpopulations of concern. * Least expensive since no interviewers are required. * Large numbers of respondents may be contacted over a large area. * Most likely to provide honest answers. * Complex technical data may be obtained if respondent takes the time to consider the questions and/or consult other sources. * Survey can cover broad areas of inquiry.	* Cannot reach people without mailing addresses. * Questions must be carefully designed to compensate for lack of personal interaction. * Questions should be limited in scope and complexity. * Requires substantial follow-up efforts or incentives to achieve reasonable response rate. * Higher number of inaccurate and incomplete responses. * May miss respondents who are illiterate, or have difficulty in understanding questions, or who cannot read the language.

5. REBUTTAL TO DR. EATON'S OPINION

Dr. Eaton largely makes the same arguments against my opinion as he did in a previous lawsuit. I have attached my response to those issues here as Appendix A.

5.1. Rebuttal to Dr. Eaton's opinion on TCE Cancer Testing

Dr. Eaton states that, since trichloroethylene (TCE) was a widely used solvent that did not undergo cancer testing, that proves that industrial chemicals were not being tested for carcinogenicity during the period of 1930–1960. The fact that Dow did not perform any cancer test shows commercial chemicals were not being tested during that period. He states:

> *Examples of other industrial chemicals produced by other manufacturers tell the same story (i.e., no carcinogenicity testing was performed in the lack of the triggers outlined above). Dow and DuPont were primary producers of chlorinated solvents such as trichloroethylene (TCE) and perchloroethylene (PCE or tetrachloroethylene), widely used in a variety of industries, including the dry- cleaning industries (Doherty, 2000a, b). In spite of being widely used with high- levels of exposure because of their volatility, these chemicals were not tested for their carcinogenic potential by either Dow nor DuPont (or any of the other manufactures of TCE and PCE). Even though manufacture and use of TCE started in the early 1930s, neither the Hartwell 1951 nor the Shubik and Hartwell 1957 compendiums list any long- term feeding studies related to*

> *trichloroethylene and TCE is not listed in the Hartwell 1941 compendium (Hartwell, 1941, 1951; Shubik and Hartwell, 1957). The first IARC Monograph on carcinogens, published in 1972, included entries for carbon tetrachloride and chloroform, but nothing on trichloroethylene (IARC and World Health Organization, 1972). An early review of TCE toxicity was provided by Shubik and Hartwell (1957). Numerous acute and subchronic studies of TCE were cited, including subchronic exposures at Dow chemical company laboratories Adams et al. (1951) as cited by Shubik and Hartwell (1957). But Dow never performed a 2- year chronic bioassay on TCE.*

Dr. Eaton is simply stating because one chemical (a widely used solvent) out of thousands that were manufactured during 1930–1960 was not tested for cancer, there was no reason that PCBs should have been tested for carcinogenicity. Dr. Eaton is arguing a point that I did not cite as a reason or trigger for why Monsanto should have tested PCBs for cancer. Although PCBs were produced in massive quantities and released into the environment, I did not state that PCBs should have been tested because of that reason. The fact is, there were no triggers for anyone to be concerned about TCE during that period, and there were multiple reasons I cited and discussed in my expert report. But before I repeat my rationale for cancer testing, I should point out some interesting contradictory facts about the above quote by Dr. Eaton that do not support his opinion.

First, it is interesting to note that Dr. Eaton states that Dow conducted acute and subchronic testing on TCE:

> *Numerous acute and subchronic studies of TCE were cited, including subchronic exposures at Dow chemical company laboratories Adams et al. (1951)*

This is in stark contrast to Monsanto's lack of concern about the toxicity testing of PCBs. As I stated in my expert report, Monsanto started PCB production in 1929, but conducted no toxicity tests on PCBs until 1969. Although Drinker, Miller, and others had conducted toxicity tests that showed high toxicity and precancerous evidence of tumors, Monsanto did not conduct such tests. [38] [39] The company did not perform any testing on PCBs until the IBT studies were started in 1969, and those were *prompted* not out of Monsanto concern about the toxicity but because the company admitted it had no toxicity data; furthermore, reports started to become publically available by 1969 that provided evidence that PCBs could be a worldwide contaminant. [40]

First, Dr. Eaton states that TCE was widely used and was volatile:

> *In spite of being widely used with high- levels of exposure because of their volatility, these chemicals were not tested for their carcinogenic potential by either Dow nor DuPont (or any of the other manufactures of TCE and PCE).*

One of the reasons TCE would not be a good candidate for cancer testing is because it is volatile and is physically on the opposite side of the spectrum with regard to its physicochemical properties compared with PCBs. In this regard, Dr. Eaton is comparing two different classes of chemicals. The reason PCBs should have been tested is because they are not volatile, and the primary exposure route is ingestion. Because TCE is inhaled, there was no concern about exposure to the general public. By contrast, PCBs posed a great health threat because they are not volatile (i.e., are persistent), which is why they constitute a worldwide contaminant even today. Furthermore, TCE is not bioaccumulative and stored in human fat tissue for decades like PCBs are. Even though PCBs were banned in 1979, nearly all Americans still have detectable body burdens of PBCs. TCE, by contrast, is very rapidly eliminated from the human body within hours. For example, ATSDR states:

> *A relatively small amount of absorbed TCE is exhaled unchanged; most of an absorbed dose is metabolized and excreted in the urine.*
>
> *After exposure to air concentrations between 50 and 380 ppm, approximately 58% of an absorbed dose appears in urine as metabolites (Monster, Boersma et al. 1976; Monster, Boersma et al. 1979). The time between TCE inhalation and urinary excretion of trichloroethanol is relatively short (biologic half-life approximately 10 hours) compared with the urinary excretion of trichloroacetic acid (biologic half-life approximately 52 hours).* [41]

As I discussed in my expert report, one of the triggers was PCBs' similarity to dichloro-diphenyl-trichloroethane (DDT). During the 1940s, Monsanto was producing both DDT and PCBs, and the FDA showed DDT was carcinogenic: [4]

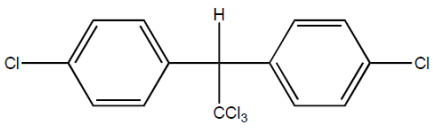
Tendency to hepatic tumor formation was, on the basis of comparison with many hundreds of rats of similar age, definite but minimal in both two-year series. Altogether, in both experiments, 4 rats each had one or more small hepatic cell tumors, from 5 to 12 mm. in diameter, paler than the surrounding liver tissue on gross examination, not sharply circumscribed microscopically, and composed of cells larger than those in the rest of the liver. Lobular architecture was almost obliterated. Mitoses were not noted. Some cells had foamy cytoplasm; some cells showed DDT changes of a degree greater than that elsewhere. Tumors of this type are not a sharply defined entity, and the question of their nomenclature cannot be treated here. They would probably be generally called ademonas because of their relative size, discrete gross appearance, and almost total loss of lobular architecture. There might be almost as much justification for considering them low grade hepatic cell carcinomas.

Eleven other rats showed varying amounts of nodular adenomatoid hyperplasia; the nodules were generally of 1 to 3 mm. diameter, and were usually noted grossly as scattered yellowish foci. Nodules smaller or less distinct microscopically were not diagnosed as adenomatoid hyperplasia. The microscopic appearance was essentially the same as in the larger tumor masses; difference in size is chiefly responsible for the difference in terminology. Nodular adenomatoid hyperplasia is almost never seen in our rat livers except after treatment with a few distinctly tumorigenic substances. About 1% of our older rats will spon-

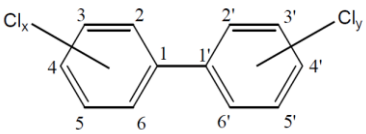
What prompted FDA to begin its chronic cancer testing was DDT's accumulation and storage in body fat for long periods of time. [4] The FDA study showed that DDT was carcinogenic, and Monsanto already knew that PCBs and DDT shared the same physical properties (fat soluble) and were similar chemically. TCE is very dissimilar to either PCB or DDT because it does not share the same physical or chemical properties as either DDT or PCBs. It does not have either a phenyl ring or a benzene ring, which were chemical triggers for conducting cancer tests based on the structure-activity relationship.

PCBs and DDT share the same chemical properties as shown below and would be expected to show the same toxicity and carcinogenicity (the structure-activity relationship), whereas TCE does not share any of the properties that were known to be carcinogenic.

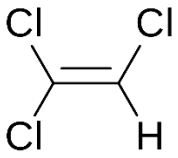
Exhibit 35. TCE Does not share the same chemical structures with PCBs and DDT Add an Exhibit heading and reference



DDT
(dichlorodiphenyl trichlorethane)



PCB
(polychlorinated biphenyl)



TCE
Trichloroethylene

The other triggering evidence included specific pathological findings by Drinker [38] and Miller [39] that were known at the time to be preneoplasic lesions that form during the early stage of tumorigenesis and were seen at about 3.5 months. The pathological features or hallmarks of early tumorigenesis that were described by Drinker, as well as by Miller, included the following:

- Hyaline inclusions or bodies
- Mitotic figures
- Granulated cells

Despite these pathological hallmarks being identified and characterized as highly unusual, Monsanto conducted no chronic toxicity testing until 1969, when it began chronic studies. The very first cancer study conducted by Monsanto showed PCBs were carcinogenic. [42]

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APPENDIX A

TABLE OF CONTENTS

LIST OF EXHIBITS

1. INTRODUCTION

I have reviewed Dr. Eaton's Expert Report in this matter. The following summarize my rebuttal opinions. I have concluded Dr. Eaton:

1. Presents numerous tables and text from polychlorinated biphenyl (PCB) cancer studies that were produced to contain false information and data, even though Monsanto admitted in 1981 that they were false and invalid;

2. Relies on numerous false and fraudulent studies to make false statements and form his conclusions about the carcinogenicity of PCBs;

3. Incorrectly states the number of positive animal tests showing cancer based on discredited histopathological diagnostic criteria developed by the National Cancer Institute (NCI) in 1975 to incorrectly conclude the number of studies showing PCBs were carcinogenic;

4. Ignores the gold standard toxicology test results on PCBs that were published by the Public Health Service in 1944;

5. Presents an incorrect and misleading framework for the generally accepted toxicology practice used to develop scientific methods of testing and protocols;

6. Incorrectly states that there were no standard practices for conducting toxicity tests until after 1970;

7. Lists and discusses the important toxicological testing criteria pre-1970 and post-1970, and all but one are incorrect due to an incomplete knowledge of historical toxicity testing;

8. Does not cite or discuss the most important milestone in the field of toxicology: the 1949 U.S. Food and Drug Administration (FDA) "Black Book" written by Lehman et al. that presents standard toxicity testing protocols developed specifically for the chemical industry to assess chemicals that could potentially contaminate food;[1]

9. Incorrectly states there were no "standard practices" developed before 1970 that could be used to test Monsanto's PCBs when, in fact, standards were available in 1949 and were specifically designed for industrial chemicals like PCBs that were being produced in massive quantities and could be released into the environment;

10. Does not consider or even acknowledge the early industrial cancer studies that were being conducted in the late 1930s by Dow, DuPont, and Bayer AG; and

11. States that there were no good standard protocols for cancer testing before 1970, but ignores the FDA cancer study for dichlorodiphenyltrichloroethane (DDT) published by Fitzhugh and Nelson in 1947 that showed DDT was carcinogenic;[2] the study presented an excellent protocol that Monsanto could have easily adopted to test PCBs, and Monsanto likely knew about this study since it started producing PCBs in 1944.

2. GENERAL COMMENTS: DR. EATON'S ASSERTIONS REGARDING "STANDARDIZED PRACTICES" AND CANCER TESTING PROTOCOLS

Dr. Eaton states that there were no "standardized" toxicity testing protocols prior to 1970; this was, presumably, his explanation for why Monsanto could not have performed chronic toxicity and cancer testing prior to 1970. The evidence upon which Dr. Eaton relies is provided in summary format in Table 12 of his expert report. In that table, Dr. Eaton incorrectly states that there were no specific standard practices for numerous study design parameters and criteria needed to conduct cancer testing pre-1970. He juxtaposed pre-1970 practices with post-1970 practices in that table and for each ad hoc criterion (there are many more he ignores), he essentially states that there were no standard criteria pre-1970. While the study criteria Dr. Eaton bases his opinion on are vitally important to planning and implementing a rigorous study design, there are others that were ignored. Nevertheless, Dr. Eaton has used this comparison to support his opinion that there were few, if any, experimental standard practices for any of his categories prior to 1970 and, accordingly, I have focused on the criteria he has identified.

3. STANDARDS OF PRACTICE

On page 72, Dr. Eaton describes the history of industrial toxicology and cancer testing. His description is largely based on a single source—a textbook chapter by Henry F. Smyth, Jr., in *Casarett and Doull's Toxicology: The Basic Science of Poisons.*[3] He does not state his process of review and analysis of historical studies or whether he even read the actual published studies from the 1900s to the 1950s. However, I am very familiar with the textbook he cites because it was the textbook I was trained with and it was *the* assigned textbook to me when I took my introductory toxicology course. It is now the very same textbook I assign to my students in the toxicology course I teach. While this textbook serves to provide an excellent *general overview* of specific topics in toxicology; it does not in any way provide a detailed historical treatise on the history of cancer testing. In other words, it is a general introductory textbook used in first-year toxicology courses that rather superficially touches on many aspects of the field of toxicology. Moreover, Dr. Eaton provides a single quote from the Smyth chapter as his major reference reliance document to suggest that cancer testing was not conducted in the early 1930s–1950s. This is incorrect and, as I have stated in my expert report, even major industrial chemical companies like Dow, DuPont and Bayer AG (which now owns Monsanto Company) were testing their products in the late 1930s to determine if they were carcinogens.

In contrast to Dr. Eaton's review of a single textbook, I have now collected and reviewed more than 200 original peer-reviewed reports on myriad aspects of cancer research. These reports involve early testing of laboratory animals starting in the late 1800s and continuing through the early 1970s. (I have been engaged in this research for over 5 years, and it forms the basis of my toxicology teaching materials.)

Based on my research and an analysis of Dr. Eaton's opinions regarding historical cancer testing, I find his opinion is biased, truncated, and a work of revisionist history, since cancer testing began much earlier than the 1970s, as did protocols underpinning such testing.

The term *standardized testing* also has a specific meaning in toxicology because it indicates that scientists and regulators are following the same procedures in order to comply with some new law or regulation that allows government scientists to compare different studies with the same

metrics. In this sense, standardization is intended to provide consistency. For chemicals that are regulated, the chemical industry must test them. However, starting in the late 1930s chemical companies were testing for carcinogenicity because they believed they had an obligation to protect both workers and the general public—not because they were required to.

It is not clear from Dr. Eaton's expert opinion, but he seems to indicate that cancer studies performed prior to 1970 are not valid or scientifically tenable. He also seems to indicate that Monsanto could not conduct cancer studies before 1970, suggesting that Monsanto was waiting for toxicologists to take the lead on standardization—and only then could Monsanto consider conducting its first cancer study in 1969. The evidence I have reviewed does not support his opinion.

Dr. Eaton states that, prior to 1970, animal cancer tests were somehow unreliable. He contrasts animal cancer testing protocols during the periods before and after 1970, stating:

> *In evaluating the state of science and how cancer testing has evolved since the 1930s, it is important to compare the state of animal cancer testing before and after standardized protocols came to fruition in the 1970s. Certain aspects of study design scientists take for granted today were not regarded as important in the 1930s. Table 12 lists these differences, which include treating the controls in the same fashion as treated animals, understanding the background incidence of disease in the studied experimental animal, and consideration of the age of animals tested, using an adequate number of animals to see a response, testing the animals for long enough periods of time (2 years), as well as numerous issues related to animal care and housing.*

Dr. Eaton's Table 12 is presented in Exhibit 1 (I discuss this table at length in following sections).

Exhibit 1. Table 12 from Dr. Eaton Report

Table 12. Animal cancer testing study design practices before and after 1970

Study Design Parameters	Pre-1970 Practices	Post-1970 Practices
Number of Dose Groups	Typically a single dose group	Minimum of three or more groups
Method of Administration (e.g., Dermal, Inhalation, Gavage, Dietary)	Dermal or inhalation exposure (assess occupational exposure)	Dietary or gavage to ensure dose
Length of Administration (How Long)	Variable	Established period of time: Lifetime ~ 2 yrs
Animal Care	Not standardized	Rigidly controlled, standardized animal medicine practices
Tissue analysis	No uniform classification system	Established classifications
Pathology review	Single pathologist	Multiple pathologists
Statistical practices	None or non-standardized	Highly standardized
Group Size	Variable	Larger numbers of animals, animals individually tracked and assessed
Species	Multiple species	Rats or mice, consistent strain or sensitive strain
Gender	Random gender selection	Both genders or most sensitive gender
Age	Varied	Studies begin at specific, young ages
Historical Controls (Summary of Control Animals)	Generally not available	An integral part of study design
Doses Administered (Total Dose and Variability Within Study Period)	May have relied on a minimum range finding study (dose could be adjusted during study)	Use of a subchronic study to set chronic dose levels (doses aren't typically adjusted)
Observations	Limited	Comprehensive
Intervals of Administration (On/Off)	Variable intervals	Continuous
Test Substance	Purity impossible to determine	Purity confirmed, contaminants identified
Source of Test Compound	Not specified	Well documented
Record Keeping	No requirements	Good Laboratory Practice (GLP) regulations
Additional Analysis (e.g., Hematology, Urinalysis)	Limited	Comprehensive analyses
Laboratory Design	Not standardized	Clean/dirty corridor systems and Standard Operating Procedures
Study Segregation	Not standardized	One study per room

Source: Eaton 2019.[4]

Dr. Eaton's table indicates a belief that cancer studies in the 1930s through the 1960s were poorly designed. It is apparent that he has not actually reviewed those studies, because many of

the carcinogens we know today were first identified as carcinogens in that period. While cancer testing protocols have improved, clearly the early cancer studies achieved what they were designed to do: identify chemical carcinogens. Nevertheless, Dr. Eaton states Monsanto could not have identified PCBs as carcinogenic prior to 1970. I have reviewed and considered his evidence and supporting rationale; I have concluded the following:

1. Dr. Eaton ignores the sole intent and purpose of using laboratory animals in cancer testing and misrepresents the concept of standardized animal cancer testing protocols as they apply to Monsanto's Aroclors.

2. Dr. Eaton incorrectly states that cancer testing standardization occurred only after 1970, even though the FDA began standardizing animal cancer testing in 1947.[2]

3. Dr. Eaton ignores the fact that (with few exceptions) hundreds of chemical carcinogens were first identified in the 1930s and 1940s with animal cancer studies and that those studies have been reaffirmed and shown to be valid to this day.

4. Dr. Eaton ignores the fact that the most widely studied group of chemical compounds selected for animal cancer testing in the 1930s and 1940s were the very same chemical compounds that were, and continue to serve as, the feedstock for all organic compounds produced in the chemical industry. All organic chemical compounds start from coal tar, petroleum, and oil.

5. Dr. Eaton ignores the fact that standardization was actually a deliberate step to ensure a particular chemical carcinogen did not slip through the cracks of testing and to guard against a false negative study in which a chemical carcinogen would be incorrectly and falsely regarded as a noncarcinogenic. For example, the number of animals that are used in cancer studies must be increased for weak carcinogens compared to strong carcinogen. PCB carcinogenicity did not require hundreds of animals because it is not a very week carcinogen.

6. Dr. Eaton does not cite any regulatory or well-established protocol(s) that he defines as a standard animal testing protocol developed in 1970.

7. Dr. Eaton ignored the fact that even Industrial BIO-TEST Laboratories, Inc. (IBT) (the contract laboratory that Monsanto hired to conduct its PCB cancer studies) did not follow any cancer testing protocol, so even under Dr. Eaton's theory, IBT's studies should not be considered as valid studies; IBT certainly did not adhere to Dr. Eaton's standard cancer testing practices in the early 1970s.

8. IBT knowingly included false and fabricated information and data in its cancer studies to make it appear PCBs were less toxic and carcinogenic than they actually were, and it submitted those false reports to Monsanto. Monsanto, in turn, submitted those fraudulent findings to U.S. EPA, the National Cancer Institute (NCI), and other scientific experts who reviewed the animal histopathology, cancer incidence rates, and other critical information important for making interpretative conclusions about the carcinogenicity of PCBs.

9. Dr. Eaton ignores the fact that, despite his conclusion that no standardized cancer testing protocols were available until the 1970s, major industrial chemical companies like Dow, DuPont, and Bayer AG were screening their chemical compounds for carcinogenicity using animal cancer tests by the late 1930s to protect both their workers and the general public.

10. Dr. Eaton fails to note that an excellent and robust animal cancer standard study design had been developed by the FDA by 1943 (published in 1947 by Fitzhugh and Nelson) when it started its DDT cancer study.[2] This study design performed as it was intended because the FDA was able to show that DDT was a carcinogen in 1947. This study was conducted more than 20 years before 1970. FDA was able to correctly conclude DDT was carcinogenic based on the generally accepted practice of applying the cancer testing protocols used in the more than 1,000 studies published by that time. The FDA's findings and conclusions have stood the test of time, and many laboratories duplicated FDA's findings and confirmed DDT is carcinogenic.

11. I have reviewed the general study design IBT implemented in 1971 cancer studies, and it was no different from the design of cancer studies that were being performed in the 1930s and 1940s. These studies were not in any way complex or sophisticated, and they required no specialized equipment or analyses that would have prevented Monsanto from conducting the same studies decades earlier. Monsanto could have performed similar cancer studies

on Aroclors in the late 1930s and 1940s. Had Monsanto conducted the tests decades earlier, I believe they would have concluded PCBs were carcinogenic.

12. Dr. Eaton has not considered that if Monsanto had simply followed the very same cancer testing protocol used by the FDA in its 1947 DDT cancer study, it would have determined that PCBs were also carcinogenic.[2]

The sole intent of long-term animal cancer studies for industrial chemicals like PCBs (that are not regulated) is to determine if they are carcinogenic. It should be stressed that *all* animal tests are designed to *screen* compounds to determine if they are carcinogenic in *animals*. Animal studies provide supporting evidence that a chemical is a human carcinogenic. We cannot perform cancer testing on humans because it is unethical to expose humans to compounds that could be carcinogenic. Therefore, it is universally accepted by toxicologists that we must screen them *before* humans are exposed and not *after* the fact. Dr. Eaton suggests that the chemical industry waited until *after* humans were exposed (whether in the workplace or general public) and that those human exposures must have produced observable human cancers before the chemical industry would perform a long-term animal cancer test. It defies logic to suggest we would test a chemical compound in rats if we already knew that the compound produced cancer in humans.

It is also important not to superimpose the current state-of-the-art in cancer testing protocols toxicologists currently use and assume cancer experts in the 1930s–1960s were ignorant, naïve, and/or untrained; to suggest otherwise is scientific hubris. Many of the compounds we know today as carcinogens were first identified in the 1930s–1960s.

It is clear that Dr. Eaton has ignored many of the early and excellent cancer studies that form the basis of our current understanding of carcinogenicity because they were not conducted under what he considers standardized protocols or methods. He tends to focus on the exceptions and not the rule.

With rare exceptions, the vast majority of chemical compounds found to be carcinogenic in the early 1930s and 1940s are still today regarded as carcinogenic. This shows that the gradual refinement of cancer testing codified in Dr. Eaton's standardization paradigm is unrelated to the goal of animal cancer testing—which is to simply test whether a chemical compound is carcinogenic.

For example, the very first animal cancer test was performed in 1915 by Yamigawa and Ichikawa when they applied coal tar to rabbit ears.[5] With prolonged exposure, cancerous growths developed, demonstrating that chemical compounds could be tested in animals. This experimental protocol sounds crude by today's standards, but it could be repeated in any university laboratory by first-year toxicology students, yielding the same results and with only a few rabbits. They did not need a standard practice protocol and their experimental design proved to be excellent for their goal and purpose. Likewise, Monsanto did not need to use thousands of animals with sophisticated expensive equipment to identify PCB as carcinogens in the 1930s and 1940s, and any qualified academic institution during that time would be well-equipped to conduct the same cancer experiment IBT conducted in the early 1970s.

As I discussed in my expert report, the sole opinion I have expressed in my report regarding historical animal cancer testing is simple: Monsanto *could have* and *should have* conducted long-term animal cancer tests in the 1930s or 1940s. The issue of when cancer testing protocols were standardized is not relevant to my opinion because the definition of standardized cancer testing is constantly evolving and being refined. Toxicologists are today relying on much more sophisticated study designs than were used by cancer experts conducting studies in 1970–1990, but that does not make the earlier studies any less relevant or wrong.

For example, Dr. Eaton presents his loose definition of a standard animal cancer testing protocol (for which he cites no reference), but fails to mention the gold standard of cancer testing developed by the leading governmental toxicology agency in the U.S.—the National Toxicology Program (NTP).[6] The NTP protocol is far more sophisticated, complex, and lengthy than Dr. Eaton's ad hoc standard protocol. The NTP protocol is extremely sophisticated, requiring many different experts from many different scientific disciplines and requires *far more* animals than Dr. Eaton's standard criteria indicate. But experiments following this protocol are extremely expensive, long, and labor-intensive to conduct. However, the NTP studies are based on the most rigorous cancer testing protocols and their findings are regarded as the gold standard among most toxicologists in the United States and around the world. The NTP is the only governmental group charged by the U.S. Congress to produce a yearly compendium identifying chemical cancer compounds. The NTP summarizes the *Report on Carcinogens* as follows (https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html):

> *The Report on Carcinogens (RoC) is a congressionally mandated, science-based public health report that identifies agents, substances, mixtures, or exposure circumstances (collectively called "substances") in our environment that pose a hazard to humans.*

The NTP was established in 1978 to:

- Coordinate toxicology testing programs within the federal government;
- Strengthen the science base in toxicology;
- Develop and validate improved testing methods.
- Provide information about potentially toxic substances to health, regulatory, and research agencies, scientific and medical communities, and the public.

The NTP standard protocol is perhaps the most detailed and rigorous that has been developed to date.[6] The reason the NTP cancer study standard protocol is important to my rebuttal opinion is because each *individual* cancer study requires more than 800 laboratory animals and was estimated to cost $2–$4 million in 2009. Obviously, these expensive and sophisticated protocols preclude most industrial and university laboratories from following the NTP cancer testing protocol. Nonetheless, many toxicologists in both academia and industry perform many cancer studies each year that are accepted in the scientific community and add valuable data and information to the catalog of identified carcinogens *yet do not follow* the NTP protocol because it would be impossible. Applying Dr. Eaton's reasoning about the importance of standardizing cancer testing protocols, all cancer testing prior to the protocol used by NTP today would be considered substandard and flawed, and the results therefore suspect, because it did not follow the most current standard protocol.

Regarding the supposed lack of a standardized approach prior to 1970, Dr. Eaton makes contradictory statements about *why* Monsanto did not conduct animal cancer studies in the 1930s, 1940s, 1950s, and 1960s. While Dr. Eaton states that standardized toxicological testing only occurred after 1970, he does not mention that standardization of any toxicology testing occurs as a result of a new law or regulation that chemical companies must satisfy. That is,

testing protocols are not standardized because the government suddenly decides that it would be a good idea. Standardized toxicological testing protocols are developed first by the government to meet the requirements of a proposed or new law or regulation. For example, the FDA first published guidance for the chemical industry to assess the toxicity of chemicals in food in 1949 (Lehman et al.); the guidance is known as the Black Book.[1] This guidance was developed in response to the 1938 FD&C act. Although the FDA had no legal authority to force the chemical industry to follow its guidance, the Agency thought it important to provide standardized testing protocols for those in the chemical industry who were planning to add chemicals to food or thought that, due to the amounts they were producing, their chemicals *could* contaminate food (PCBs fall in this latter category).

The importance of impending or new laws or regulations that force the government to standardize toxicological testing cannot be overemphasized with regard to Dr. Eaton's opinion because it specifically addresses a need by the government—not by academic or industrial cancer researchers. The point at which the government standardizes testing does not indicate that, prior to that point, scientific cancer experts were conducting cancer studies on chemicals in a random ad hoc fashion; it simply marks a point in time when the government instructs the chemical industry on how it should conduct experiments to *satisfy new or anticipated laws*. In this sense, new standards are government instructions that apply to laws or regulation. Furthermore, the FDA did not create standards in a vacuum; it was aware of the more than 1,000 cancer studies that had been published in peer-reviewed scientific journals by the 1950s, and those studies provided a road map of generally accepted practice at the time.

Dr. Eaton's opinion regarding the importance of a standardized protocol is contradictory. He acknowledges that Monsanto began performing cancer tests in 1969, yet then says that a company would have had no standardized testing protocols to conform to until years after that time.

I have reviewed dozens of Monsanto memos, reports, and documents pertaining to the company's toxicological testing; none of them state or even suggest that the reason Monsanto waited until 1969 to start testing PCBs for carcinogenicity was because a standardized methodology was unavailable before that time. At the very least, Monsanto must have known by

1947 that scientifically tenable cancer testing protocols had been developed for industrial chemicals because that was when FDA (Fitzhugh and Nelson, 1947) published its findings showing one of Monsanto's products (DDT) was carcinogenic in animals. [2]

The standards Dr. Eaton is suggesting were available only post-1970 would have had little impact on identifying carcinogens like PCBs and DDT. In fact, FDA's 1947 study showing DDT was carcinogenic should be proof that cancer studies performed at that time were sufficiently powerful to reveal PCB – a similar compound -- was carcinogenic. [2]

3.1. Dr. Eaton incorrectly states that "standardized" cancer testing protocols were only available after 1970

Dr. Eaton did not cite, discuss, or consider for his opinion the most important historic milestone in toxicity testing: The 1949 FDA Black Book.[1] It is hard to overstate the importance of this FDA guidance document, since it was prepared for the chemical industry to use in designing a series of robust toxicological tests of the products chemical companies were producing. It represents the overall approach and experimental paradigm that academic and industrial toxicologists use to test all chemical compounds. It is the foundation of toxicological testing that toxicologists still use today. The fact that Dr. Eaton does not even *cite* this document appears to be an indication that his review of historical toxicity testing is superficial. In the sections below, I present the salient aspects of these original standardized and comprehensive testing protocols because Dr. Eaton did not do so. That is, he did not present a discussion of this document, and that failure is the impetus for including the following facts and information.

3.1.1. Overview of the FDA Black Book

Starting in 1938, with the passage of the FD&C, the FDA was the lead regulatory agency that oversaw applications for, and safety of, new drugs. The FD&C recommended the chemical industry to perform toxicity tests on any new drugs prior to being sold. The FDA developed general guidelines for the industry, but there were no designated standards.

The first toxicity testing standards were developed by the FDA in 1949 as part of the implementation of the FD&C.[1] The standards called for a battery of toxicity tests that the

chemical industry should conduct. This was the first comprehensive testing framework to be issued as a guidance document for the chemical industry, and it was intended to be used by the entire chemical industry. This guidance is referred to as the Black Book. The protocols are detailed in the article Procedures for the Appraisal of the Toxicity of Chemicals in Foods (Lehman, 1949). The protocols presented in this document were prepared by the some of the leading scientists of the day, including Drs. Lehman, Laug, Woodard, Draize, Fitzhugh, and Nelson, who were all FDA scientists and were experts in their fields. The protocols are detailed in sections on: (1) chemistry, (2) acute toxicity, mechanism and site of action, (3) allergic responses, (4) subacute and chronic toxicity, reproduction and paired feeding studies, (5) biochemistry, and (6) pathology. Although these topics were finally standardized by the FDA in 1949, these protocols represented the state-of-the-science that scientists were following in the early 1940s. They represented the cumulated scientific methods that were being used as generally accepted practice in toxicology well before 1949.

3.1.2. Important Standardized Toxicity Testing that Preceded the Black Book

Numerous study designs had been developed prior to publication of the 1949 Black Book.[1] For example, the FDA had already designed and implemented its DDT cancer study and published the study design and findings in 1947.[2]

In addition, FDA scientists Woodard and Calvery published a list of standard toxicity tests as early as 1943 in the article Acute and Chronic Toxicity-Public Health Aspect.[7] This document discusses a battery of toxicity studies, and it was intended as a general toxicity study protocol.

In their report, Woodard and Calvery listed the following types of studies that were necessary to conduct "well-controlled toxicological evaluations," emphasizing the need for testing "new" chemicals or "older substances which have not been properly tested," stating:

> *However, with the newer substances, or even with the older substances which have not been properly investigated, it will be necessary to design and carry out well-controlled toxicological investigations, and when the studies are complete, make proper evaluations of the data obtained.*

Their procedures were intended to be used to ensure the safety of synthetic materials that were being produced in greater numbers each year, with a special mention of keeping water supplies safe from contamination:

> *As our population becomes more urban and our consumption of synthetic materials grows with each year, the problem of acute and chronic toxicity becomes increasingly important to the public health. Such concentration of population necessitates handling, transportation, and storage of foodstuffs. This in turn has resulted in the use of preservatives and stabilizers, and in the danger of contamination of foods in manufacturing, refining, and packaging. The exposure of the majority of the population to ever-increasing quantities of synthetic products in foods, drugs, cosmetics, household items, clothing, etc., extends the possibility of chemical sensitizations and poisonings. Urban areas require central water supplies which must be so chosen and maintained that they will not contain harmful impurities.* [emphasis added]

They listed the following battery of toxicological tests that were necessary to prove a chemical compound safe for human exposure (Exhibit 2):

Exhibit 2. Excerpt from Woodard and Calvery: Toxicological Tests Needed to Prove a Chemical Is Safe for Human Exposure

A. Pharmacodynamics
Blood pressure; respiration; heart rate; organ perfusion; isolated tissue preparations; etc.

B. Acute toxicity
Dosage response curves on three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances.

C. Subacute toxicity
Large daily doses to one or more species for six to 12 weeks; microscopic pathology.

D. Chronic toxicity
Three or more species; at least one species for the life of the animal; several dosage levels graduated to produce from no effect up to marked lesions, and possibly shortening life span; microscopic pathology.

E. External effects
Sensitization; skin irritation; mucous membrane irritation.

F. Special studies
Reproduction; hematology; absorption and excretion; distribution and storage; effect of diet.

Source: Woodard and Calvery 1943.[7]

It is important to note this battery of toxicology testing protocols was available in the early 1940s and that one of the most important features of the testing protocols was chronic *lifetime* animal testing.

Woodard and Calvery emphasized that, by 1943, laboratory animal breeding programs and animal testing had become standardized to ensure reproducible and consistent laboratory testing results. The also stressed the importance of including control animals:

> *With the above information, we can now more intelligently plan a chronic experiment. As a matter of fact, if the subacute experiments have been properly started, they may in some cases simply be extended to cover a longer period of time. In any event, the experiment should be conducted on three or more species for the lifetime of at least one of them. Rats, dogs, mice, and monkeys are usually good chronic toxicity subjects. Since the life span of a rat is relatively short-two to three years- and since the rat has been well standardized in many laboratories, this animal is probably the best in every respect for lifetime chronic studies. In such experiments it is well to use several dosage levels of equal gradation from the dose sufficiently high to cause marked lesions, possibly shortening the life span of the animal, to a dose sufficiently low that there are no observable differences between the experimental and control animals.* [emphasis added]

Woodard and Calvery also state that multiple species should be used and that several species including "rat, mouse, and guinea pig are well suited for this, since these animals have been quite well standardized." FDA also stressed that "several dosage levels" be used and the histopathology compared to control animals. They also provide actual examples of FDAs *cancer* studies and emphasized the importance of conducting *long-term* chronic exposures to determine if a chemical compound is carcinogenic:

> *The value of such long term investigations is well illustrated in the results obtained by Yoshida who fed orthoaminoazotoluene to rats for 200-300 days to produce true experimental liver tumors. It has also been well illustrated in our own laboratory by studies on the glycols. Ethylene glycol, for example, was fed in the diet of rats at levels of 1% and 2%. Kidney and bladder stones appeared in both series of animals. No stones were observed, however, in animals that failed to survive longer than 15 months. Another example is the production of neurofibromas on the ears of rats fed crude ergot. These tumors first appeared*

> *after about 12 months and within 24 months were present on all animals receiving 5% of ergot in the diet.* [emphasis added]

Just from this brief discussion, it is clear that the FDA was following a standardized protocol in its cancer testing, which represented the state-of-the-science prior to 1941. The cancer studies were designed to test whether a compound was carcinogenic, and the study design showed they performed well, based on the authors' description.

Woodard and Calvery also note that it is of particular concern to carefully evaluate the toxicity of chemical compounds that bioaccumulate and produce cumulative toxicity because the compounds are stored in the body and are only slowly eliminated:

> *The absorption, excretion, distribution, and storage of a toxic agent will often guide one in an estimation of its probable effect. If there is an indication of storage of the toxic substance, one should watch for cumulative toxicity. If the material is rapidly eliminated from the animal, and no storage occurs, the toxicity from cumulation likely will not be as serious as the chronic toxicity which may result from the passage of the poison through the system.* [emphasis added]

This particular section and warning perfectly describes the types of chemicals (like PCBs and DDT) that should be of particular concern in toxicology testing because both bioaccumulate and are stored in fat tissues in the body for long periods of time.

Woodard and Calvery also importantly stresses that *all* chemicals be tested *before* they enter the "economy of man" to preclude both accidental and intentional exposures:

> *Extensive investigations carried out on different species of animals are to our minds absolutely essential before a substance should be introduced into the economy of man. The experience and information thus obtained will then enable one to, interpret observations made on human beings whether accidentally or industrially exposed to such a substance, or whether intentionally exposed under carefully controlled clinical conditions.* [emphasis added]

This is the first instance I am aware of in which a governmental group of scientists stresses the importance of the precautionary principle, which is based on knowing the toxicity of a chemical

compound *before* it is released into the environment or, as Woodard and Calvery call it, the "economy of man."

Woodard and Calvery identify many of the critical variables that must be carefully evaluated and controlled when interpreting the results of the battery of toxicology studies they propose (0). These include many of the same variables that Dr. Eaton states are important in standardizing cancer studies, which he claims were only addressed after 1970. These were identified by the FDA in 1943.

Exhibit 3. Excerpt from Woodard and Calvery: Interpretation of Toxicity Data

Interpretation of Toxicity Data

AFTER the toxicological data have been made available, the next major problem which presents itself is the interpretation of these data in terms of their applicability to the public health. The factors involved in making such an interpretation are numerous and complicated. In order that they may be more easily visualized, it seems advisable to present some of them in outline form, followed by a brief general discussion:

A. Variation between species
   1. Response of different species to a single substance.
   2. Response of different species to different substances. Contributory factors to the above differences in response are relative surface area and organ capacity, and differences in absorption, metabolism, detoxification, and excretion.

B. Variation between individuals in the same species
   1. Normal distribution and heterogeneity of the population.
   2. Physiological condition.
      (a) Age, sex, weight.
      (b) External environment.
      (c) State of physical exertion.
      (d) Pregnancy and lactation.
      (e) Presence of food in gastro-intestinal tract.
   3. Pathological condition.
      (a) Renal, cardiac, and hepatic insufficiency, etc.
      (b) Presence of infectious organisms.
      (c) Nutritional deficiencies.
   4. Multiple exposures.

Source: Woodard and Calvery 1943.[7]

Finally, Woodard and Calvery issue a cautionary note about extrapolating toxicity data derived from animal studies in which only "normal healthy" animals are used directly to humans because that could lead to underestimating the risk a chemical compound could pose to a heterogeneous population of humans that may not all be in great health and whose members may have preexisting medical conditions:

> *So far, we have discussed reactions on normal individuals. Our experiments have been carried out using normal healthy animals. But in the public which may be exposed, there are many who are most certainly not normal, healthy persons. We must consider then a rather large number of persons who are so unfortunate as to suffer from pathological conditions or disease. The yearly vital statistics are ample proof of the number of people who have cardiac, renal, or hepatic insufficiencies or cancer.*

In 1944, FDA scientists also published a similar battery of standardized toxicological tests for new drug applications (van Winkle et al. 1944) in which they cite earlier FDA publications dealing with standardized toxicology tests (Exhibit 4).[8]

These were much more detailed study designs, but as with previous FDA guidance documents, no law required any chemical company to test the chemicals they were producing. Although PCBs were not intended as drugs, these protocols could be used to design a toxicity study for any chemical. Animal studies always precede human studies, so the documents presented the basic framework to those types of tests. Overall, these documents illustrate the sophistication and extent of toxicological testing that had developed by the early 1940s. Many of these tests still form the backbone of FDA's animal toxicology requirements.

Exhibit 4. Excerpt from van Winkle et al.: Objectives of Various Test Categories

(A) *Biochemistry.*—General properties of drug, including solubility, stability; studies of absorption, reabsorption, fate, distribution and excretion of the drug; quantitative data on these points where possible; mode of detoxification (excreted unchanged, oxidized, reduced, acetylated?); effect on enzymes, blood and tissues; chemistry of body fluids and tissues; production of toxic products during course of metabolism.

(B) *Pharmacodynamics.*—Local: Tests of irritation on skin, eye, alimentary canal; intradermal irritation, sensitivity or anesthesia; tests of protoplasmic depression or toxicity, and reversibility of effects on cilia, nerve trunks, mucosa; hemolysis, antihemolysis and blood pigment changes.

Systemic: Action on blood pressure, respiration, muscles, nervous system, cardiac functions, secretions, temperature, voluntary activity, organ perfusion, isolated tissues; effects of vasomotor agents, proteins, fats, metals, solvents and other agents on the actions of the drug; cumulative effects; development of tachyphylaxis; quantitative and qualitative differences in action in different species of animals.

(C) *Experimental Functional Pathology.*—Effects in experimentally induced pathologic states, e. g. smooth muscle spasm, hypodynamic hearts, fibrillations and arrhythmias, hypertension, respiratory depression, edema, shock, burns, anemias.

(D) *Chemotherapeutic.*—Effects in preventing specific experimental infections; effects in combating experimental infections or actions of toxins; antagonists of chemotherapeutic agents, e. g. pus, serum, tissue products; distribution in inflammatory states, e. g. meningitis, dermatitis; minimal effective dosage (ED50).

Source: van Winkle et al. 1944.[8]

3.2. The History of FDA Guidance and Regulations

3.2.1. ***The FDA Black Book***

Dr. Eaton's opinion is based on an incomplete historical review of toxicological and cancer testing in the 1930s through the 1960s. In fact, Dr. Eaton does not mention or cite in his expert report what is perhaps *the* most important milestone in historical toxicology testing: the U.S. FDA Black Book.[1] The FDA was the first governmental agency to document, in detail, standard

protocols for the entire battery of toxicological testing, including long-term cancer studies. These governmental standard protocols were published as: Procedures for the Appraisal of the Toxicity of Chemicals in Foods (Lehman et al. 1949).[1] The authors were among the most highly respected and widely published scientists and toxicologists of the time and had been conducting and publishing studies using the same standard protocols starting in the early 1940s. In this sense, the testing protocols detailed in the FDA Black Book were not a *newly* developed battery of toxicological testing procedures but a compendium of protocols that were being used throughout the 1940s. For example, Drs. Fitzhugh and Nelson began their chronic long-term DDT cancer study in 1943, although it was not published until 1947.[2]

Dr. Eaton's omission of the Black Book is an indication that his review of historical cancer testing is surficial at best. The Black Book is widely known throughout the field of toxicology and is recognized as presenting the first standardized toxicological testing study designs (I review this important milestone as part of my graduate toxicology course in the introductory lecture). In fact, publication of the Black Book is listed as a key milestone on the FDA web page that chronologically lists the Agency's major accomplishments in U.S. food and drug law:[9]

> *Milestones in U.S. Food and Drug Law History*
>
> *1949*
>
> *FDA publishes guidance to industry for the first time. This guidance, "Procedures for the Appraisal of the Toxicity of Chemicals in Food," came to be known as the "black book."*

Dr. Eaton correctly states that Monsanto was under no regulatory obligation to perform any long-term cancer study on PCBs because it was not a drug, food additive, or pesticide used on crops, stating:

> *It is important to note several points about this excerpt from Dr. Smyth's textbook chapter:*
>
> *1. This pertains to industrial chemicals not intended for use as pharmaceuticals, food additives, pesticides used on food crops for which other guidelines were developed. PCBs were never marketed and sold for any of these purposes.*

> *2. There is not even a suggestion that two-year bioassays be conducted for the purposes of evaluating potential cancer-causing properties of the materials not used as pharmaceuticals, food additives, or on-crop pesticides*

This particular statement is highly misleading and is false by omission. Dr. Eaton fails to mention that there was *no* regulation in 1949 for *any* industrial chemical company to conduct *any* toxicological test—including long-term animal cancer testing–on *any* chemical that was intentionally developed to be a food additive or was an unintentional food contaminant (like DDT or PCB). The only law that existed in 1949 was the FD&C that was passed by Congress in 1938. The FD&C did not require that any chemical be tested. Moreover, FDA's Black Book *does not* contain any term such as *must* or *shall*. This fact is widely known in the field of toxicology. For example, the introductory textbook I assign to my first-year graduate toxicology students–*Casarett and Doull's Toxicology: The Basic Science of Poisons* (6th Edition)—states as much.[10] This is the same textbook Dr. Eaton cites as the "widely-acclaimed toxicology textbook." In Chapter 34, which covers Regulatory Toxicology, Dr. Merrill states:

> *The oldest of the major health regulation laws, the FD&C Act, was enacted in 1938 and covers food for humans and animals, human and veterinary drugs, medical devices, and cosmetics.*

Dr. Merrill notes that the 1938 FD&C law was an amendment of the original Pure Food and Drug Act of 1906, which contained two provisions:

> The first forbids the marketing of and food containing *any added poisonous or deleterious substance which may render it injurious to health…*
>
> The second forbids the marketing of foods containing *nonadded [sic] toxicants that make them "ordinarily injurious to health."* [no emphasis added]

He stresses:

> *Neither of these original provisions required premarket approval; the FDA had the burden of proving that a food was, in the legal vernacular, adulterated.* [emphasis added]

The only amended part of the 1938 FD&C law that provided for regulatory oversight was for truth in advertising *foods* and not *industrial chemicals.* For example, in a detailed discussion of the law, the FDA states:[10]

> *The FD&C Act authorized three kinds of food standards--identity, quality, and fill of container. In 1939, the first food standards were issued for canned tomatoes, tomato purée, and tomato paste. The standards looked like a recipe of listed ingredients. The next standards were for jams and jellies. Junod says, "By 1957, standards had been set for many varieties of foods such as chocolate, flour, cereals, bakery products, milk, cheese, juices, and eggs."*

Obviously, if no chemical company was required by any regulation to conduct any toxicity test in 1949 and it was up to FDA to identify food contaminants that could be poisons (only after they were already released into the environment), then the FDA *did not* write the Black Book just for the regulated chemical community. The Black Book was published as a guidance document for *all of the chemical industry*. FDA's very title of the guideline indicates it was not narrowly directed toward a small segment of industry. The Black Book was officially titled, Procedures for the Appraisal of the Toxicity of Chemicals in Foods.[1] As specified by the official title, the Black Book had nothing to do with food additives, which were not regulated for approximately another decade with passage of the FDA's 1958 Delaney Amendment. Therefore, Procedures for the Appraisal of the Toxicity of Chemicals in Foods could apply to Monsanto's PCBs, which were being released in massive amounts into the environment and were later found to contaminate the U.S. food supply.

The FDA intended the Black Book to be used as a guide for chemical industry to test any industrial chemical manufactured in large quantities and to adopt the testing methods detailed within to prevent harmful chemicals from entering the food supply. The Agency specifically noted that it was for "chemicals likely to contaminate foods:"

> *The body of knowledge accumulated as the result of the above described studies has for its purpose the determination of the relative safety of the chemicals proposed for addition to foods or likely to contaminate foods.* [emphasis added]

The introduction to the Black Book was written by Dr. Lehman, who was the Chief of the Division of Pharmacology of the Food and Drug Administration. Dr. Lehman emphasizes two

important points about how critical chronic toxicity testing is for food contaminants compared with toxicological testing for drugs. First, in contrast to drug testing in which exposures are usually limited, human ingestion of food contaminants lasts a lifetime, and U.S. citizens would be "forced" to ingest them daily. Dr. Lehman wrote:[1]

> *As a general rule, drugs are administered for short periods of time so that the duration of the toxicological insult to the body is limited. Even though a medicament may possess undesirable side effects, these usually are outweighed by the therapeutic actions, and the use of the drug can be justified on this basis. On the other hand, when a chemical is added to foods, its ingestion literally is forced upon the individual, and this may continue throughout his lifetime. Under these circumstances, the approach to the appraisal of its safety for use is somewhat different from that for a drug. More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs.* [emphasis added]

Dr. Eaton is correct in stating that PCBs were never considered as intentional food additives. However, by 1949, DDT had been released in massive quantities into the environment (not intentionally added to food products), and those releases were known at that time to have resulted in contamination of the U.S. food supply. For this reason, Lehman's second emphasis in the Black Book introduction appears have been a direct and explicit effort to not only focus on chronic studies to make a determination about chemical toxicity but to change the basic concept and definition of poisons and toxicity that many chemical companies were using to show their chemicals were nontoxic. Lehman singled out chemicals that bioaccumulate and are stored in the body to show they are more toxic than chemicals that are known to be highly toxic based on acute exposures. In this effort, Lehman specifically used DDT as the example chemical compound that was thought to be entirely safe and harmless by the public and scientific communities simply based only on the acute toxicity studies (defined by the LD50) that had been performed. With a simple calculation example comparing a known poison and DDT, the FDA showed this assumption was false and that fat-soluble compounds like DDT are readily absorbed and stored in the body and that chronic exposures increase the body burden to toxic levels even with minute daily intakes (thought to be safe). Lehman provided the following simple example:

> *More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs. For example, carbolic*

> *acid (phenol) is practically synonymous with the term "poison," and DDT has been considered a quite harmless substance. It has been demonstrated in this laboratory that rats can ingest a diet containing one per cent carbolic acid for a long period of time without producing much harm to the animals. Under similar conditions, rats are injured when the diet contains 0.001 per cent DDT, which indicates that DDT when consumed for long periods of time is at least 1000 times more poisonous than carbolic acid.* [emphasis added]

Finally, the Black Book lists all the sequential toxicity tests that are included in any health evaluation, and it presents the same scheme applied today by most academic and industrial toxicologists. At the end of the Black Book, FDA presents an outline of all the standardized tests it discussed in detail in the body of the publication to make it easy for the chemical industry to follow. (See Exhibit 5.)

Exhibit 5. FDA Black Book Outline of Standardized Tests

The salient features of the technics and procedures as presented may be outlined as follows:

I. Chemistry
- 1. Solubility
  - a. Water, oils, and fats
  - b. Physiological fluids
- 2. Chemical characterization
  - a. Composition and constitution
  - b. Stability, purity
- 3. Quantitative detection in micro amounts

II. Acute Toxicity and Pharmacodynamics
- 1. Oral LD_{50} in several species
  - a. Variations between species
  - b. Variations between individuals in same species
  - c. Variations between sexes
  - d. Effect of concentration, age, weight, season, environment, and nutritional state
- 2. Pharmacodynamics
  - a. Intravenous toxicity for determining effect on cardiovascular, respiratory, and gastro-intestinal systems, etc.
  - b. Effect on specialized organs and tissues

III. Allergic Response
- 1. Sensitizing reactions in guinea pigs

IV. Subacute and Chronic Toxicity
- 1. Subacute toxicity (2 to 4 months' feeding)
  - A. Rats
    - a. Control
    - b. A low level of feeding about 10 times amount of the chemical as proposed for use in foods
    - c. An intermediate level which may or may not produce an effect on the animal
    - d. The highest level which the animal can tolerate
  - B. Dogs
    - a. Control
    - b. Low level at which no effects may be observed.
    - c. Something less than the maximum tolerated level. Effects may be noted
    - d. A near maximum level. Injury can be expected
- 2. Chronic (long-term) toxicity
  - A. Rats
    - a. Control
    - b. A level of feeding which will give at least 100 times the concentration in the diet as proposed for food use.
    - c. A level which may or may not produce injury
    - d. The highest tolerated amount which can be fed. Injury can be expected.
  - B. Dogs or monkeys
    - a. Control
    - b. A low level which will produce no effects
    - c. A middle level which may or may not produce injury
    - d. A high level approaching the tolerated dose
- 3. Reproduction studies
  - a. Effect of chemical fed continuously through three generations of rats
- 4. Paired feeding

V. Biochemical studies
- 1. Absorption, distribution, and excretion
- 2. Detoxification mechanism and fate
- 3. Organ function tests
- 4. Studies on enzymes

VI. Pathology
- 1. Gross examination of organs and tissues
- 2. Detailed histological examination of organs and tissues of control and experimental animals

[The End]

Source: Lehman et al. 1949.[1]

3.2.2. Jacobs and Hatfield Historical Reconstruction of Toxicity Testing Standards

My opinion that FDA's Black Book provided detailed procedures and protocols by (at least) 1949 is supported by other scientific experts who have similarly traced the chronological sequence of cancer testing by reviewing the actual scientific publications and regulatory documents to reconstruct cancer testing milestones, as I presented in my expert report. For example, Jacobs and Hatfield (2012) conducted a similar comprehensive review of when industrial cancer testing protocols were standardized and note:[11]

> *In the United States, with the passage of the Food and Drug Act of 1906, the Food and Drug Administration (FDA; then known as the Bureau of Chemistry under the US Department of Agriculture) was charged with the responsibility for preventing the adulteration or misbranding of foods and drugs that were marketed to the public. Beginning in 1938, the Federal Food, Drug, and Cosmetic Act gave regulatory powers to the FDA, requiring, among other things, that new drugs be clinically tested and proven safe prior to being sold. The FDA offered guidelines for such studies, but there were no designated standards.*

Jacobs and Hatfield support my opinion that, in 1949, the FDA *did* create the first *standardized* guidance document available for the chemical *industry* to follow. Most importantly, they highlight the fact that the Black Book contains a section written by Dr. Fitzhugh that stressed the importance of long-term studies and their design (Fitzhugh published the DDT long-term cancer study with Nelson in 1947):

> *The FDA first published guidance for industry for assessing the toxicity of chemicals in food in 1949. This guidance was referred to as the ''black book'' and included a contribution by O. Garth Fitzhugh on the subject of long-term studies and their design.* [emphasis added]

Jacobs and Hatfield note that the Black Book states two species (rodent and nonrodent) should be used:

> *Fitzhugh suggested that for long-term feeding studies, 2 species should be investigated: the albino rat would be studied for a lifetime of about 2 years, and a nonrodent second species (dogs or monkeys) would be studied for at least 1 year.*

They also note that the Black Book calls for extensive and comprehensive histopathological examination of all the major organs:

> *Biochemical and hematology evaluations were to be made at 3-month intervals during the chronic study. At the end of the study, autopsies were to be performed, along with weighing of the principle organs and preservation of tissues for microscopic examination. The pathology evaluation was described in further detail in the black book by Arthur Nelson, indicating that tissues to be evaluated included lung, heart, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary bladder, testis or ovary, prostate or uterus, thyroid, parathyroid, submaxillary salivary gland, 4 levels of brain, hypophysis, bone, bone marrow, and voluntary muscle.*

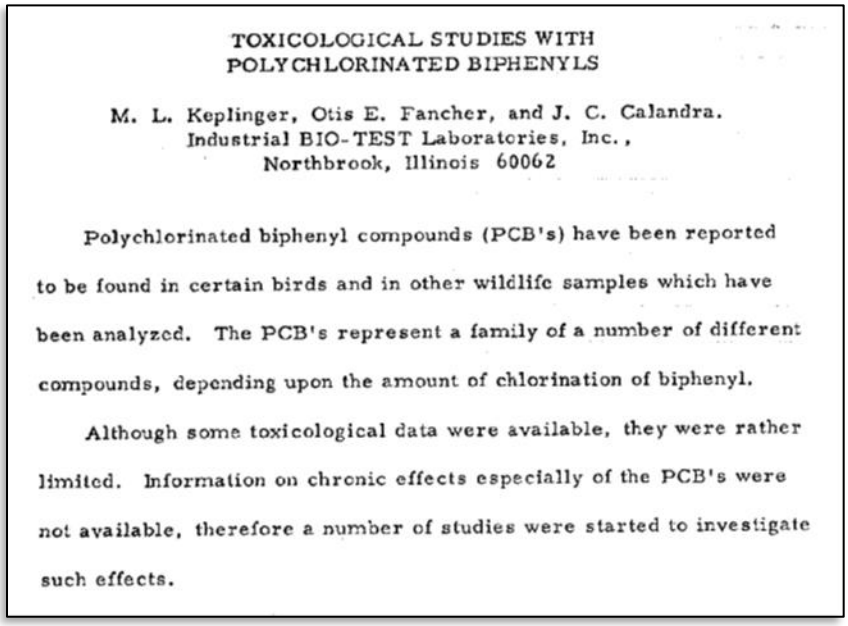
3.3. Monsanto's Lack of Chronic Toxicity Studies

As I discussed in my expert report, Monsanto must have known by 1949 that PCBs, like DDT, were fat soluble (Monsanto manufactured both). However, Monsanto continued to rely on its acute toxicity studies (LD50 studies) as its sole basis for assuming PCBs were not toxic—a conclusion Monsanto communicated to its customers. Dr. Eaton's opinion that Monsanto conducted hundreds of toxicity studies misrepresents the toxicity information that was necessary to correctly evaluate the toxicity of PCBs. Monsanto conducted zero chronic studies to determine the chronic toxicity of PCBs until 1969.

My opinion is that Monsanto should have conducted chronic cancer tests in the 1940s, but certainly after 1949 when the FDA issued guidance to the chemical industry. Monsanto did not perform any toxicity studies, including chronic exposure and cancer studies, until 1969. This fact is supported by Dr. Calandra, who was the president of IBT. IBT was the contract laboratory that conducted the very first chronic study in 1969s as a prelude to cancer studies that were initiated in 1969. Dr. Calandra states the reason for starting those chronic studies was that no chronic toxicity study had been conducted for PCB. In a Monsanto memo (TOXSTUDIES0996), Drs. Keplinger, Francher, and Calandra stated (Exhibit 6):[12]

> *Information on <u>chronic effects especially the PCBs were not available</u> therefore a number of studies were started to investigate such effects.* [emphasis added]

Exhibit 6. Excerpt from IBT Memo From Keplinger, Fancher, Calandra



TOXICOLOGICAL STUDIES WITH
POLYCHLORINATED BIPHENYLS

M. L. Keplinger, Otis E. Fancher, and J. C. Calandra.
Industrial BIO-TEST Laboratories, Inc.,
Northbrook, Illinois 60062

Polychlorinated biphenyl compounds (PCB's) have been reported to be found in certain birds and in other wildlife samples which have been analyzed. The PCB's represent a family of a number of different compounds, depending upon the amount of chlorination of biphenyl.

Although some toxicological data were available, they were rather limited. Information on chronic effects especially of the PCB's were not available, therefore a number of studies were started to investigate such effects.

Source: IBT, Toxicological Studies with Polychlorinated Biphenyls (Bates 0531555; TOXSTUDIES0996)

It should be noted that in reviewing what Monsanto is defining as "toxicity" tests conducted from 1929 through the mid-1960s (before they conducted their first chronic testing) and comparing them with the FDA Black Book list were not toxicity tests. The only tests Monsanto conducted for PCBs were LD50 studies to determine the amount of PCBs that were lethal in the rat (and only on rats, rather than on the several species necessary and stated in the 1949 Black Book—so even the LD50 studies were not conducted according to the standard). Monsanto also conducted brief allergic sensitization studies and very short irritant studies on the skin and eye to evaluate worker exposures.

3.4. Dr. Eaton: Table 12 (Dr. Eaton Report, page 74)

3.4.1. Pre- and Post-1970 Designations

I have carefully reviewed Dr. Eaton's Table 12. In the first column, he lists what he calls the "Study Design Parameters." He then lists what he believes the state-of-the-science was for each

of those parameters in the "Pre-1970" (column 2) period, which he juxtaposed next to the "Post-1970" (column 3) corresponding criteria. It is not clear why he arbitrarily chose 1970 to divide the two periods. As I stated previously, standardized protocols are (with few exceptions) developed to meet the requirements of a new *government* law or regulation or by a governmental scientific body like the Centers for Disease Control and Prevention (CDC) or the National Toxicology Program (NTP). I am not aware of any new regulatory laws, requirements, or standardized protocols developed in 1970. There were certainly no new U.S. Environmental Protection Agency (EPA) laws or regulations because the Agency was not created until 1970. FDA's standard procedures were developed in 1949—although they have continuously been further refined over the decades.

I assume that Dr. Eaton believes the 1970 date is important only because that is when Monsanto finally started its chronic toxicity studies, including cancer studies. Dr. Eaton appears to be attempting to show that Monsanto somehow could not have conducted long-term cancer studies *before* 1970 because there were no standards.

3.4.2. Dr. Eaton Table 12 vs. FDA Black Book Guidelines

I carefully reviewed Dr. Eaton's summary table for each of the Study Criteria Parameters listed in the Pre-1970 Practices column and compared those to what was detailed in the 1949 FDA Black Book guidelines. Obviously, 1949 was well before 1970, so I focused on the Black Book to determine whether Dr. Eaton was correct and when standardized protocols were first available for Monsanto or any other industrial chemical company to use in order to test their chemical products in a consistent and effective manner. To show that the FDA had developed standard practices available for industry as early as 1949, I have added a fourth column to Dr. Eaton's table (designated as *Dr. DeGrandchamp*). Furthermore, in order to preclude any bias from my review and interpretation of the Black Book, I have inserted the specific information quoted from that publication. With this approach, I was able to evaluate Dr. Eaton's summary opinion for his pre-1970 analysis, as well as whether the criteria he listed as being available only post-1970 were actually available in 1949. (See Exhibit 7)

Exhibit 7. Dr. DeGrandchamp Modification of Dr. Eaton Table 12: Animal Cancer Testing Study Design Practices

(Pre-1970 and post-1970: Dr. Eaton; 1949: Dr. DeGrandchamp)

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
Number of Dose Groups	Typically a single dose group	Minimum of three or more groups	**RAT: MINIMUM 3 DOSE GROUPS** **NON-RODENT DOG OR MONKEY: MINIMUM 3 DOSE GROUPS** "Dosage levels are kept adjusted to the body weight changes."
Method of Administration (e.g., Dermal, Inhalation, Gavage, Dietary)	Dermal or inhalation exposure (assess occupational exposure)	Dietary or gavage to ensure dose	**INGESTION:** **FOOD CONTAMINANTS ARE EATEN FOR A LIFETIME** "The substance may be administered by stomach tube [gavage], capsules, or by mixing with the animals' food."
Length of Administration (How Long)	Variable	Established period of time: Lifetime ~ 2 yrs	**ESTABLISHED PERIOD OF TIME: LIFE SPAN IN RAT ~2 YRS - RATS SACRIFICED AT 2 YEARS.** **FOOD CONTAMINANTS MUST UNDERGO LIFETIME CHRONIC TOXICITY TESTING:** "On the other hand, when a chemical is added to foods, its ingestion literally is forced upon the individual, and this may continue throughout his lifetime." "More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs."
Animal Care	Not standardized	Rigidly controlled, standardized animal medicine practices	**RIGIDLY CONTROLLED:** "Rats are housed individually in an air conditioned laboratory and records kept of all observations for the duration of the experiment."
Tissue analysis	No uniform classification system	Established classifications	**EXTENSIVE FDA DISCUSSION OF PATHOLOGICAL HALLMARKS OF CANCER DESCRIBED EARLIER—1947** (Fitzhugh and Nelson 1947)
Pathology review	Single pathologist	Multiple pathologists	**COMPREHENSIVE PATHOLOGICAL EXAMINATION OF TREATED AND CONTROL ANIMALS:** "*No matter what amount of pathological study is done, at least a little and sometimes much of its value is lost if it is not done with*

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS *Lehman et al. 1949*[1]
			good control material, and against a background of experience"[no emphasis added] **ALL PATHOLOGICAL EXAMINATIONS SHOULD BE BLIND WITH PATHOLOGIST IGNORANT OF TREATED AND CONTROL TISSUES:** "An excellent stimulus to objectivity in examination is for the pathologist not to know, until a preliminary report has been made, which are control and which are treated animals. "1. Gross examination 2. Thorough microscopic morphological histopathological pathology and histology required 3. Pathological examination "should be detailed enough to show the lowest dosage level of the chemical capable of producing it in even the slightest degree." 4. At minimum "detailed microscopic (and, of course, gross) examination of enough animals to give statistical significance to the results. 5. Pathological examination of organs: lung, heart, liver, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary bladder, testis (or ovary), prostate (or uterus), thyroid, parathyroid, submaxillary salivary gland, four levels of brain, hypophysis, bone, bone marrow, and voluntary muscle. 6. Histopathology: routine stains, special stains for identification of pigments, fat stains on frozen sections, stains for glycogen, and imprints or smears of bone marrow. "By detailed study is meant autopsy and gross examination of all experimental and control animals, except perhaps those in which the experimental period has been only a day or two, and microscopic examination of all major organs and tissues in sufficient numbers to make reasonably certain whether the chemical is or is not causing injury or change in any of them. If there is any effect, then the examination should be detailed enough to show the lowest dosage level of the chemical capable of producing it in even the slightest degree." ORGANS TO BE EXAMINED: "A list of organs routinely examined in our dogs may be of some help as a guide. These include lung, heart, liver, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
			bladder, testis (or ovary), prostate (or uterus), thyroid, parathyroid, submaxillary salivary gland, four levels of brain, hypophysis, bone, bone marrow, and voluntary muscle." REASON HISTOPATHOLOGY REQUIRED "The most legitimate objection that may be made to the inclusion of microscopic pathological study in a chronic toxicity experiment is that if growth, mortality, and reproduction are unaffected, and if gross examination at autopsy shows no difference from the controls, then microscopic examination would according to the objector) in all probability show no difference. There are several reasons why it should be done nevertheless." THREE REASONS ARE STATED. "Generally speaking, slight but significant microanatomical effects frequently will be found at a dosage level where mortality and weight are unaffected."
Statistical practices	None or non-standardized	Highly standardized	**PATHOLOGICAL LESIONS IN DOSED AND CONTROL GROUPS ARE STATISTICALLY ANALYZED, DOCUMENTED AND STATISTICAL SIGNIFICANCE CALCULATED**
Group Size	Variable	Larger numbers of animals, animals individually tracked and assessed	**RAT: 80 RATS PER STUDY** "In the rat experiment, at least four groups of animals, each consisting of a minimum of ten males and ten females, are employed and distributed as follows: (a) a control group, (b) a group on a diet containing 100 times as much of the ingredient as is proposed for use in food, (c) a group fed a diet containing the highest tolerated amount of the substance, and (d) a group given an intermediate dosage level." **NON-RODENT:** **24 DOGS/MONKEYS PER STUDY** A minimum of 3 male and 3 females in each of 3 dose groups and a control group "Three animals each on four dosage levels. These are assigned" to (a) a control group, (b) a group on a low level which will produce no damage, (c) a group on a high level which approaches the tolerated amount, and (d) a group on a middle level which may or may not produce injury.

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
Species	Multiple species	Rats or mice, consistent strain or sensitive strain	**RATS HAVE BEEN STANDARDIZED:** "The albino rat has been a standardized animal and has a life span of about two years, it is the most convenient test object for long-term feeding experiments" **NONRODENT SPECIES:** DOG Or MONKEY Nonrodent species required.
Gender	Random gender selection	Both genders or most sensitive gender	**BOTH GENDERS ARE DOSED**
Age	Varied	Studies begin at specific, young ages	**DOSING IS STARTED IN YOUNG WEANLING RATS**
Historical Controls (Summary of Control Animals)	Generally not available	An integral part of study design	**CONTROLS ARE ALWAYS USED FOR SPONTANEOUS TUMOR INCIDENCE IN EACH STUDY** *"Tissue alterations resulting from the administration of- drugs or chemicals are frequently not of a new or special type; rather, there is often but an increase in the incidence or degree of some type of abnormality already present in that particular laboratory strain of animal.* [original emphasis] "The above is but another way of saying that enough animals must be examined to give the observations statistical significance, and that the common "spontaneous" lesions absolutely cannot be disregarded." "For example, older rats on control diets may show a relatively slight degree or incidence of a chronic nephritis or nephrosis. Their mates fed a certain chemical may show the same histological changes in the kidney, but the process, on the average, will be of greater intensity or frequency." [emphasis added] "Control animals in experiments involving repeated subcutaneous .injections, stomach tubing, and so on, should not be simply untreated animals, but should be given injections and tubings as similar as possible to the test group, except of course for the presence of the chemical to be tested."
Doses Administered (Total Dose and Variability Within Study Period)	May have relied on a minimum range finding study (dose could be adjusted during study)	Use of a subchronic study to set chronic dose levels (doses aren't typically adjusted)	**SUBACUTE/SUBCHRONIC STUDIES MUST PRECEDE CHRONIC STUDY TO SET CHRONIC DOSING LEVELS**

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
			"The two series of animals are fed their respective diets for a period of <u>two to four months.</u>" "The first consideration for a chronic study is a "pilot" experiment designed to serve as a guide in planning a long-term experiment. Beginning with weanling rats, several dosage levels are administered for periods of two to four months, thus covering the period of rapid growth. Four groups of weanling rats of the same sex are probably the minimum which can meet the requirements."
Observations	Limited	Comprehensive	**COMPREHENSIVE** "Observations should be made on the rate of growth, food and water intake, fertility, Mortality, general appearance, and behavior of the experimental animals. Blood and Biochemical studies should be made during the experimental period. Upon completion of the feeding period, all animals should be autopsied for gross changes in the organs, the principal organs should be weighed, and tissues preserved for histopathological study. Animals showing significant loss in weight, the development of a tumor, or other evidences of severe abnormality during the experimental period should be sacrificed and the tissues preserved for histopathological study. Tissues of animals dying within the experimental period also should be preserved for study. With these facts in mind, a general plan which is designed to throw light on this question is given below." **MANY ADDITIONAL DETAILS PROVIDED** [emphasis added]
Intervals of Administration (On/Off)	Variable intervals	Continuous	**NO ON/OFF DOSING NECESSARY: HUMANS ARE FORCED TO EAT FOOD CONTAMINANTS ENTIRE LIFETIME**
Test Substance	Purity impossible to determine	Purity confirmed, contaminants identified	**SOLUBILITY IN FATS AND OILS MUST BE DETERMINED AS WELL AS IMPURITIES:** "The most important single physical characteristic of a compound is its solubility, not only in aqueous media, the common basis of physiological fluids, but also in fats and oils. <u>So much hinges on this property of solubility that it frequently spells the success or failure of an otherwise promising compound</u>." "The seriousness of this lack can be brought into even sharper relief when we consider how necessary a good quantitative method is to the proper evaluation of a compound: (1) Determination of solubility by simple

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
			physical means alone is frequently impracticable. (2) No control operation in a manufacturing plant is reasonably secure from error without an adequate chemical method which ensures that its product be of uniform composition, free from impurity, and the amount of the compound in question held within precise limits. (3) It is impossible to assemble information on the biochemical behavior of a compound, discussion of which will be considered in another section." **CHEMICAL PROPERTIES MUST BE DETERMINED:** "This point of view is based chiefly on the fact that it is the correlation of chemical, physical, biochemical, and toxicological knowledge about a compound which is necessary in order to evaluate its safety properly."
Source of Test Compound	Not specified	Well documented	**SOURCE OF TEST COMPOUND DETERMINED BY CHEMICAL MANUFACTURE**
Record Keeping	No requirements	Good Laboratory Practice (GLP) regulations	"Records kept of all observations for the duration of the experiment. A larger number of rats per group [than the minimum stated] and more dosage levels of the substance under study will aid in the interpretation of results." **GLP REGULATIONS WERE NOT DEVELOPED UNTIL 1978** GLP was only created following the U.S. EPA/FDA audit of Industrial BIO-TEST Laboratories (IBT) studies in which several hundred studies contained deliberate fraudulent data and information.
Additional Analysis (e.g., Hematology, Urinalysis)	Limited	Comprehensive analyses	**COMPREHENSIVE ANALYSIS:** 1. Determine: absorption, excretion, storage, detoxification mechanisms, 2. Hematology 2. Urinalysis 3. Molecular Mechanism: "Depending upon the individual case, these experiments may involve studies on isolated tissues or organs, careful pharmacodynamics, electrocardiograms, electroencephalograms, chemical antidotes, chemical studies of blood pigments, isolated loop or pouch studies, renal clearance, etc." determination are made at intervals of about three months on representative animals in each group."

Dr. Eaton **STUDY DESIGN PARAMETERS**	**Dr. Eaton** **PRE-1970 PRACTICES**	**Dr. Eaton** **POST-1970 PRACTICES**	**Dr. DeGrandchamp** **PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS** *Lehman et al. 1949*[1]
			IDENTIFY CHEMICAL THAT BIOACCUMULATE OR ARE STORED IN THE BODY "Consider compounds E and F of essentially equal acute toxicity but on subacute oral exposure lasting three weeks, compound E shows greater toxicity. Examination of the tissues of the animals shows marked storage of compound E. with little or none of compound F. Here storage in the tissues can be regarded as a potential hazard, and explains the increase in subacute toxicity of compound E over F. Compound E would therefore be excluded from consideration." [emphasis added]
Laboratory Design	Not standardized	Clean/dirty corridor systems and Standard Operating Procedures	**STANDARD OPERATING PROCEDURES USED** "Rats are housed individually in an air conditioned laboratory and records kept of all observations for the duration of the experiment." [emphasis added]
Study Segregation	Not standardized	One study per room	**SEE ABOVE**

3.5. Pre-1970 Cancer Study Design Practices

It is important to note that all of Dr. Eaton statements about which standards were developed pre-1970 lack veracity. Moreover, Dr. Eaton's pre-1970 statements are gross oversimplifications regarding *standardization practices* and suggest that cancer studies during that time were simply scattershot. In fact, academic and industrial toxicologists pre-1970 would *never* have simply reviewed voluminous published studies cancer studies and somehow formulated a cancer testing protocol by amalgamating all the cancer studies and distilling them into a study design to test a chemical for carcinogenicity. Nor would they just randomly select a published study and follow the experimental design. That is not how any scientist would proceed during the pre-1970 period, nor would it be true today. Scientists review extensive published studies and typically select the best and most robust study design to follow.

Dr. Eaton suggests that Monsanto could not have conducted any cancer study pre-1970 because not all study designs were *identical.* This defies not only the standard generally accepted practice a toxicologist would follow to find the best verified study protocol with which to conduct a cancer study for an industrial chemical, it also defies logic. Cancer studies were expensive and time consuming, and labor-intensive. They lasted 2 years, so no toxicologist would even consider starting a cancer study before extensively reviewing the published literature to design the most cost-effective and scientifically tenable testing protocol. Dr. Eaton's opinion is simply wrong because he creates a false choice between conducting a cancer study using a *bad study design* or refusing to conduct any study (the option Monsanto chose).

Had Monsanto investigated performing a cancer study on PCBs in the 1940s, it would have only needed to find *one* robust study with a solid, well-described protocol and preferably one that was *relevant* to an industrial chemical. I have discussed many such studies in this rebuttal report and in my original expert report, but one prime example of a solid study in the 1940s was the 1947 Fitzhugh and Nelson FDA DDT cancer study.[2] This study was an *FDA-published study*.

I have reviewed the 1947 FDA study; it is a robust analysis showing that DDT was a carcinogen and control animals were used to assess spontaneous tumors. All Monsanto needed to do was adopt the FDA study design and implement it; Monsanto would then have found that its Aroclors were carcinogenic—just like the FDA found DDT to be carcinogenic.

3.5.1. GLP Practices Were Not Established Until 1978

Dr. Eaton correctly states that *Good Laboratory Practices* (GLP) programs were not developed before 1970. However, it is not clear that he realizes why this particular fact is so important to this case. He notes that GLPs were not established before 1970, but he fails to appreciate that the *primary reason* they were first established is because of the fraudulent and false studies IBT submitted to the government. Moreover, the relevance of this fact is that IBT was also the *sole* laboratory Monsanto used to conduct all of its PCB cancer studies in the early 1970s; those tests were also shown to be deliberately fraudulent, containing much false information and data, and were submitted to U.S. EPA.

The U.S. EPA and FDA were forced to standardize and codify GLPs in 1978. As I mentioned above, the only notable difference between the post-1970 standard practices and those I listed above directly from the 1949 FDA Black Book is that there were no GLP procedures when the Black Book was published. There is no indication from the hundreds of historical publications I have reviewed that there was any concern in the 1930s through the 1960s about dishonest scientists or testing laboratories conducting fraudulent studies and producing false documents that purported to show a chemical was safe when it was not (although there were likely scientists who did). This perception changed after the U.S. EPA-FDA audited the laboratories and records from the IBT laboratories. IBT conducted hundreds of toxicity studies for the chemical industry, and hundreds were found to be *deliberately* fraudulent studies based on *intentionally* included false data and information about their test results. These fraudulent IBT studies were submitted to the government, which resulted in many untested and potentially toxic chemicals being used as pesticides; this could have posed significant health risks to the U.S. food supply and the general population because their toxicity was unknown.

In 1983, the U.S. EPA provided a summary of its review of IBT's blatant disregard of generally accepted laboratory practices that all other laboratories followed and the fraudulent reports submitted by IBT to the government.[13] The scandal shook the chemical industry and governmental agencies:

> *The IBT scandal shook the industry and governmental regulators. Obviously, steps had to be taken, not just to deal with the IBT situation itself, but to ensure*

> *that data providing the foundation of regulatory decisions in the future are adequately prepared and scrutinized. Thus, another result of the IBT case was the establishment in 1977 of a joint EPA-FDA audit program to help ensure that another IBT situation has not occurred and will not in the future.* [emphasis added]

Dr. Seaton from the FDA provides some details on the IBT debacle and what U.S. EPA and the FDA found during their audit in a 2017 presentation to the Society of Toxicology (Dr. Eaton and I are both members) titled, *An Update on FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies Proposed Rule.*[14] The details Seaton provides on the history of GLPs and IBT's role and standard operating practices in triggering the GLP supports my opinion and shows Dr. Eaton is incorrect for the following reasons:

1. GLPs were first developed in 1978 (not 1970) because of IBT's fraudulent studies;

2. GLPs were developed in 1978, well after Monsanto already began conducting cancer studies;

3. The inspection of IBT's laboratories revealed animal toxicity testing conditions were appallingly dirty, with standing water on the floor. This disproves Dr. Eaton's opinion that after 1970, cancer studies were conducted under clean and carefully controlled conditions in which toxicology testing laboratories kept meticulous and reproducible testing records. This is at least not true in the case of the IBT studies.

Dr. Eaton's Table 12 seems to suggest that by arbitrarily selecting the 1970 time point, Monsanto's IBT PCB cancer studies were conducted under the GLP protocols, when this would have been impossible because GLP were not established until well after Monsanto submitted its IBT reports to the government.

In 2014, the U.S. Government Accountability Office issued a report to Congress (*Pesticide Safety: Improvements Needed in EPA's Good Laboratory Practices Inspection Program*) on the current status of the GLP to evaluate any improvements in the laboratory inspection process.[15] This report presents a short summary of the history of the GLP program, focusing on why formal GLPs were developed in the first place. The GAO notes that U.S. EPA and FDA have each developed their own GLP standards. It was necessary to develop these GLPs to address a very

distressing period in the field of toxicology that is well-known to most toxicologists and involved the submission of false and fraudulent reports by IBT. This was the laboratory that conducted the 1971 series of Monsanto PCB studies and submitted those reports to U.S. EPA and other scientists. IBT was responsible for all long-term cancer testing studies conducted on PCBs for Monsanto. As a result of the EPA and FDA investigations of IBT, several hundred studies were invalidated:[15]

> *EPA and FDA have each developed their own GLP standards to address problems found with laboratory studies submitted for the agencies' review. Investigations by these agencies in the mid-1970s revealed that some studies had not been conducted in accordance with commonly accepted laboratory practices… In 1983, EPA published its GLP standards for pesticide toxicology studies, and in 1989, EPA extended the standards' coverage to include nearly all research data supporting pesticide registrations under FIFRA.*

The U.S. EPA and FDA established these GLP procedures only after discovering the *deliberate* fraud in IBT testing procedures and false reports:[15]

> *EPA and FDA have each developed their own GLP standards to address problems found with laboratory studies submitted for the agencies' review. Investigations by these agencies in the mid-1970s revealed that some studies had not been conducted in accordance with commonly accepted laboratory practices. For example, according to an industry representative, one of the first laboratories to attract regulatory and media attention was Industrial Bio-Test Laboratories (IBT), a contract toxicological research laboratory that conducted much of the U.S. toxicological testing at the time. As a result of EPA's and FDA's investigations of IBT, several hundred studies were invalidated because of deliberate fraud, and hundreds of chemicals had to be retested. Specific findings included poor recordkeeping, testing conducted by untrained and unqualified personnel, and data fabrication. For example, data were submitted on rats that had previously been reported as deceased.* [emphasis added]

Accordingly, Dr. Eaton may be correct in stating that some laboratories followed *common laboratory practices,* but they did not follow GLP procedures until after they were codified in 1978.[14] More importantly, IBT, *in particular,* did not follow either GLP or common laboratory practices particularly with regard to the PCB cancer testing.

In his presentation to Dr. Seaton reconstructs the history that led to the GLP being developed and IBTs role in the following summary:

Industrial BIO-TEST Laboratories (IBT)

- *1975, FDA received a tip that there were problems with tests submitted to FDA.*
- *The medical officer found study data was 'unbelievably clean', no rats on 2-year study developed cancer.*
- *The medical officer found enough deficiencies to warrant an inspection.*
- *Visit to IBT in April 1976: "What we found there is enough to make your hair stand up."* [emphasis added]

IBT did not collect terminal blood and urine samples, which Dr. Eaton states was standard practice, but neither did they keep reliable testing records, which he states was also *standard practice* post-1970:[14]

"Magic Pencil Study"

- *Terminal blood and urine samples were not collected.*
- *Draft data tables for the blood and urine assessments were blank, as expected.*
- *However, the final report not only had values reported, but had the technical writer's name written in. All of those results had been fabricated.* [emphasis added]

Although Dr. Eaton indicates that post-1970 studies were conducted under carefully controlled laboratory conditions, IBT's studies were conducted under such dirty and appalling conditions with such little concern for the well-being of the laboratory animals' health that the animals actually suffered and died. These practices invalidate the IBT studies. Furthermore, as a toxicologist who has conducted many toxicity studies and cared for laboratory animals, I can

state that IBT's animal care borders on unnecessary animal abuse. Dr. Seaton describes the following:

> ***"The Swamp"***
>
> - *System designed for automatic watering and flushing waste from cages rarely worked properly.*
> - *Faulty nozzles sprayed the room with a continuing mist. The floor was at times submerged under 4 inches of water.*
> - *Technicians only entered the room wearing rubber boots.*
> - *Clogged water nozzles and drain hoses drenched some rats in a cold spray, while others died of thirst.* [emphasis added]

As a result of the above horrific descriptions of IBTs testing procedures and deceptive record keeping, 71% of the IBT studies were deemed invalid:

> ***Regulatory Action***
>
> - *FDA and EPA reviewed compounds that relied on IBT for data in support of safety.*
> - *Called into question the reviews of more than 200 pesticides, many were retested at manufacturer's expense.*
> - *618 of 867 (71%) of studies audited by the FDA were invalidated for having "numerous discrepancies between the study conduct and data".* [emphasis added]

This indicates that by relying on the false IBT pesticide studies, U.S. EPA unknowingly approved more than 200 pesticides that were used on food products and had never been tested for toxicity.

In addition to the above discussion of IBTs role in prompting regulatory agencies to develop the GLP, I have also reviewed the transcript of the 1991 PCB trial (WATER_PCB-00056547) in

which IBT laboratory assistant toxicologist Mr. Philip Smith testified that some of the above statements were true and correct as they relate to IBT's Monsanto PCB studies of Aroclor 1260, 1254, and 1242 in the early 1970s.[16] Smith personally worked on these studies at the direction of Dr. Paul Wright, the section head of toxicology who was later indicted and convicted of crimes relating to IBT's fraudulent testing activities. Smith's testimony also shows Dr. Eaton's opinions regarding post-1970 standard practices are incorrect at least with respect to Monsanto's IBT PCB cancer testing studies. For example:

1. Dr. Eaton stated that animal observations during the studies were comprehensive. Mr. Smith invalidates Dr. Eaton's opinion because Mr. Smith testified that many of the animals were not even weighed during the study. Furthermore, at the end of the study, he was instructed by Dr. Wright to simply make up animal weights based on historical weight data from other studies. Animal weights are a sensitive and critical indicator of an animal's overall health. Weighing animals during a chronic cancer study is routine, and this metric is carefully monitored during the entire study period. These measurements are so critical to chronic studies that a 10% decrease in body weight is conventionally considered *a toxic effect by itself.* Body weight is also critical in dosing, because dosing is *fundamentally based* on body weight. Simply put, without the body weight, the amount administered to an animal cannot be calculated.

2. Dr. Eaton stated that GLPs were followed post-1970 with regard to the overall design of the study.

Mr. Smith notes that this was not true for the IBT–Monsanto studies. IBT followed egregious testing protocols that included, most importantly, not noting that PCB-treated animals died at a high rate. Mr. Smith notes that the survivability was very poor, stating, *"There were very few animals that survived the length of the study."* In addition to the obvious fact that animals died at a high rate (and this information was falsified in IBT's records), Mr. Smith's statement is diametrically opposite from what Dr. Eaton stated with regard to the number of animals necessary to conduct a standard cancer study. First, Dr. Eaton stated that large numbers of animals are necessary for cancer studies. While IBT may have *started* with a large number of animals (which it did not, as I discuss below), IBT did not have many animals that survived the length of the study. Second, Dr. Eaton stated that statistical analysis was *highly standardized*,

which is a false statement on the face of the facts. Highly standardized analyses require a large number of animals, but are completely worthless if most animals die and cannot be examined.

1. Dr. Eaton also stated that good recordkeeping was standard practice post-1970, but neither the animal weights (as discussed above) nor animal deaths were recorded by IBT in their post-1970 studies.

2. Dr. Eaton also states that GLP post-1970 studies carefully observed animals, and a comprehensive histopathological evaluation of their organs was conducted.

Mr. Smith's testimony refutes this for the IBT PCB cancer studies. He notes that not only comprehensive pathological evaluations were not conducted on some animals but that it was not possible to do so. He testified that when animals died during the study:

> *That there were many animals that were so badly decomposed that they were worthless for pathological examination…I would say 60 percent of the animals either had—were too badly decomposed or there was no record of them leaving the studies. They just disappeared.*

Finally, according to Mr. Smith's testimony, the deviations from GLP listed above for the IBT studies were neither unique nor isolated. In response to a direct examination question of whether Mr. Smith regarded the Monsanto IBT PCB studies as *shameful or irregular*, Mr. Smith responded:

> *At the time that study was done, no. It was pretty well standard operating procedure for everything.*

*3.5.2. **Dr. Eaton Relies on IBT False Reports***

For all the reasons presented in the above section, I believe that any of Dr. Eaton's statements or opinions directly or indirectly based on any IBT–Monsanto memo, document, conclusions, or toxicological testing reports should be considered scientifically untenable and disregarded. In 1981, Monsanto (MONS213337; Further discussed in section 3.6.3) also came to the same conclusion that the IBT studies did not follow a testing protocol and was an invalid study:[17]

> *Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a, b, c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals. Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers.* [emphasis added]

The following numerous sections summarize some of the citations, statements, and opinions in Dr. Eaton's report where he cites or relies on Monsanto's IBT studies. Since the IBT studies were fraudulent, any opinion based on these studies should be considered *not scientifically tenable and should be disregarded.*

3.5.2.1. Dr. Eaton Presents the IBT Studies as Not Showing Cancer (Page 40)

The following is Table 4 from Dr. Eaton's Report (0).

Exhibit 8. Table 4 from Dr. Eaton Report: Summary of 2-Year Carcinogenicity Bioassays Completed on Commercial Mixtures of PCBs, 1971

Table 4. Summary of 2-year carcinogenicity bioassays completed on commercial mixtures of PCBs

Year	Species and strain	Test group numbers	Dose groups (ppm)	PCBs studied	Positive for cancer (M, F)*	Reference
1971	CR Albino rats; males and females	8 groups; 50 per group	0, 1, 10, 100	Aroclor 1242 Aroclor 1254 Aroclor 1260	No, No No, No No, No	(IBT, 1971a) (IBT, 1971b) (IBT, 1971c)

Source: Eaton 2019.[4]

3.5.2.2. Dr. Eaton Compares IBT Studies to Historical Cancer Studies (Page 41)

The IBT studies were fraudulent and this statement makes a comparison to those studies:

> *It is important to note, however, that the 'positive' Brunner/Mayes study utilized a formulation of Aroclor 1254 that was manufactured by a different process than had been used prior to 1974 and had considerably higher amounts of DL-PCBs, compared to 'older' Aroclor 1254 formulations used in the NCI 1977 study and the 1971 IBT study (Kodavanti et al., 2001). The DL-PCB 'TEQ' value for the Aroclor 1254 lot used in the Brunner/ Mayes study was 11 times higher than the TEQ value of Aroclor 1254 that was used in the largely 'negative' NCI 1978 and IBT 1971 studies (Kodavanti, et al., 2001).*

3.5.2.3. Dr. Eaton States that Monsanto Had No Reason to Conduct Any Cancer Test; Nevertheless, It Contracted with IBT to Conduct the First (Fraudulent) 2-Year Cancer Study (Page 92)

It is not clear why Dr. Eaton is stating that 2-year cancer bioassays have 'seldom been done" because the 1949 FDA Black Book states this is a standard protocol. Dr. Eaton goes on to state that IBT did not detect carcinogenic activity in their cancer studies, which is not correct. IBT did detect carcinogenic activity despite presenting false data in their reports.

> *Testing requirements could conceivably include a requirement for a 2-year cancer bioassay, although this has seldom been done. Thus, given the absence of any of the triggers noted above, and the complete absence of any indication from workplace monitoring that PCBs had increased cancer risk among workers, Monsanto had no reason to conduct a 2-year carcinogenesis bioassay. In fact, they were not under any obligation to do so when they contracted with IBT in the late 1960's to conduct the first ever 2-year rodent carcinogenicity study with Aroclors, which did not demonstrate carcinogenic activity in that study.*

3.5.2.4. Dr. Eaton Presents a Lengthy Discussion of the "Negative" Findings of the IBT Report (Page 174)

Dr. Eaton presents a lengthy discussion of the "negative" cancer results from the IBT study that should be discredited from his opinions.

- IBT (1971b) – Monsanto contract study on Aroclor 1254

- Table A3- 1. Histopathology of the liver of rats treated with Aroclor 1254

3.5.2.5. Dr. Eaton Assesses "Time to Tumor" Discussion (Page 183)

It is not clear why Dr. Eaton would rely on "time to tumor" (which is more routinely called latency period) when Dr. Eaton states there were no tumors.

> *3. Summary of 'Time to Tumor' information in these studies:*
>
> *IBT Studies – no useful 'time to tumor' data were provided in these studies. But there were also no tumors found, even at the end of the study, so these are largely non-informative as to when liver tumors might first appear.*

3.5.2.6. Dr. Eaton Summarizes IBT False Tumor Incidence Rate (Page 186)

In Exhibit 9, Dr. Eaton has relied on IBT incidence rates as his evidence that there were many studies published that did not show Aroclors were carcinogenic. Dr. Eaton's conclusions should therefore not be considered scientifically defensible. In addition the table appears to be incomplete or wrong. Monsanto's Memo (MONS043459) state that the early Kimbrough incident rate of "neoplastic nodules" and "hepatocellular carcinomas" was 170/180 animals not 26/184 as presented in Dr. Eaton's table. The entire table and any conclusions from the table should be discredited.

Exhibit 9. Table A3–5 from Dr. Eaton Report: Summary of Tumor Incidence from 2-Year Rat Bioassays on Various Aroclors at 100 ppm

Table A3- 5. Summary of tumor incidence from 2 year rat bioassays on various Aroclors at 100 ppm

100 ppm Aroclor 2 yr studies – Excess liver tumors- (controls were subtracted from total observed in treated)

Study, strain	Aroclor	Months	# males	# females	A+C/total M	C/total M	A+C/total F	C/total F
IBT (1971b), S-D	1254	23-24	35	35	0/11 (0%)	0/11 (0%)	1/14 (7%)	0/14 (0%)
IBT (1971a), S-D	1242	23-24	35	35	0/6 (0%)	0/6 (0%)	0/14 (0%)	0/14 (0%)
IBT (1971c), S-D	1260	23-24	35	35	0/10 (0%)	0/10 (0%)	0/15 (0%)	0/15 (0%)
Kimbrough, et al. (1975), Sherman	1260	23	0	184	-	-	26/184 (14%)	26/184 (14%)

Source: Eaton 2019.[4]

3.5.3. Number of Dose Groups

The following is FDA's summary of the dosing scheme for DDT. It refutes Dr. Eaton's statement that the number of dose groups pre-1970 was typically a single dose group. Clearly, FDA used more than one dose level in the 1947 Fitzhugh and Nelson study.[2] In fact, the FDA tested five dose levels and 12 rats per dose level (which was even more than the protocol suggested in the 1949 Black Book[1]):

> ***PART I. TWO-YEAR EXPERIMENTS.***
>
> *Method. Two experiments were conducted in which groups of weanling rats (21 days) from our colony of Osborne-Mendel strain were started on diets containing a commercial preparation of DDT composed of 81.8% p,p isomer and 18.2% o,p isomer. In the first experiment, started early in 1943 when our supply of DDT was small, 5 groups of 12 male rats were fed on diets containing respectively 0, 100, 200, 400 and 800 p.p.m. DDT incorporated in a 10% corn oil solution.*

Fitzhugh and Nelson continued their DDT cancer study to include an even greater number of animals:

> *In a second experiment, started about a year later, 7 groups of 24 rats, equally divided between the sexes, were fed on diets containing respectively 0, 200, 400, 600 and 800 p.p.m. DDT incorporated in a 10% corn oil solution, and 600 and 800 ppm. dry DDT for comparison with the oil solutions.*
>
> *RESULTS. Since the second experiment involved a much larger number of animals than the first, the following discussion of results will be confined to the former except that mention will be made to any differences which occurred in the two experiments.*

3.5.4. Animal Care

Contrary to Dr. Eaton's claims, animal housing, care, and observations were the same as we use in today's studies, with both body weights and food consumption closely monitored. Dr. Eaton stated that this was not standard practice until after 1970. Fitzhugh and Nelson state:[2]

> *All animals were kept in individual cages in a room with controlled temperature and humidity and were given free access to their respective diets and water. Body weights and food consumption were determined at weekly intervals.*

The rats were closely monitored for any change in body weight since that is a sensitive indicator of toxicity, and this was FDA standard practice in 1943. (See 0.) The reason I included the FDA table is to show how standardized the careful monitoring of animal weights was by 1943 and that it was already recognized as a critical component of any chronic lifetime animal cancer study.

Exhibit 10. Table 1 from Fitzhugh and Nelson 1947: Weight Gain in Rats Fed Diets Containing DDT

TABLE 1

Mean gain in weight of rats fed diets containing DDT (second experiment)

TIME	DOSAGE OF DDT	SEX	NO. OF ANIMALS	MEAN GAIN IN WEIGHT
months	*p.p.m.*			
3	0	M	11	310.2 ±13.3
		F	12	205.3 ± 6.8
	200	M	12	300.8 ± 9.5
		F	12	203.7 ± 6.8
	400	M	12	316.6 ± 5.3
		F	12	177.3 ± 6.4†
	600	M	12	279.9 ±11.4
		F	12	178.8 ±60.0†
	600 Dry	M	12	280.0 ± 9.9
		F	10	176.7 ± 4.1†
	800	M	12	273.7 ±14.8
		F	12	172.8 ± 7.7†
	800 Dry	M	10	255.7 ± 8.5†
		F	9	177.2 ± 7.6†
12	0	M	10	486.6 ±18.9
		F	11	293.5 ±10.7
	200	M	9	488.1 ±26.5
		F	10	282.0 ±10.9
	400	M	10	537.8 ±24.2
		F	9	253.7 ±10.8*
	600	M	11	481.4 ±23.2
		F	5	240.4 ±14.9*
	600 Dry	M	11	463.6 ± 8.7
		F	3	238.7 ± 4.4†
	800	M	10	473.7 ±21.0
		F	1	
	800 Dry	M	6	459.8 ±12.9
		F	0	

* $p < .05 - > .01$.
† $p < .01$.

Source: Fitzhugh and Nelson 1947.[2]

I have presented the FDA 1947 table of rat weights to show how important this information is to a toxicologist and to show that it was obviously standard practice by that date. This is noteworthy because IBT did *not* consider weighing rats to be a standard operating procedure in the PCB cancer studies IBT conducted for Monsanto in 1971, which is in the post-1971 period defined by Dr. Eaton. Instead of carefully and routinely weighing the rats in the PCB studies, IBT simply waited until the completion of the study and just *fabricated* the animal weights

(Glenn Brown trial testimony from October 28, 1991;[16] I discuss this further below). IBT presented this false information in its reports.

In addition, the FDA closely monitored the organ weights of liver, kidney, and spleen. This was FDA's standard practice in 1943, contrary to Dr. Eaton's opinion. (See Exhibit 11.)

Exhibit 11. Table 3 from Fitzhugh and Nelson 1947: The Effect of Chronic DDT Ingestion on Various Organ Weights

TABLE 3

The effect of chronic ingestion of DDT on the weight of the livers, kidneys and spleens of rats

DOSAGE OF DDT	SEX	NO. OF RATS	MEAN WEIGHT (GRAMS PER KGM. OF BODY WEIGHT)		
			Liver	Kidneys	Spleen
p.p.m.					
0	M	6	25.6 ±2.9	6.6 ±0.5	1.1 ±0.2
	F	7	32.7 ±3.5	7.4 ±0.4	1.7 ±0.3
100	M	4	32.2 ±1.6	7.4 ±0.5	1.6 ±0.1
200	M	7	33.2 ±2.6	6.3 ±0.3	1.9 ±0.2
	F	9	48.7 ±3.8†	8.5 ±0.4	2.1 ±0.4
400	M	6	39.9 ±2.9†	6.8 ±0.2	1.4 ±0.4
	F	7	42.7 ±2.3*	8.3 ±0.8	1.7 ±0.4
600	M	7	41.4 ±3.5†	8.5 ±0.5*	2.0 ±0.4
	F	4	67.3 ±3.3†	9.1 ±0.5*	2.3 ±0.7
600 Dry	M	5	44.1 ±6.1*	8.5 ±0.3*	1.3 ±0.6
	F	4	60.6 ±2.1†	9.2 ±0.7*	1.8 ±0.4
800	M	8	47.3 ±3.7†	8.3 ±0.4*	1.6 ±0.2
800 Dry	M	4	44.2 ±1.5†	8.7 ±0.5*	2.0 ±0.3

* p. <.05 – >.01.
† p. <.01.

Source: Fitzhugh and Nelson 1947.[2]

I show this table because the increase in liver weight should have been considered one of the "triggers" (to use Dr. Eaton's term) for Monsanto to conduct a similar cancer study for PCBs. The pathological descriptions of PCB- and DDT-damaged livers were very similar between the FDA DDT study of 1947 and the Drinker PCB studies from the 1930s. For example, the FDA notes that the DDT rat livers had approximately *doubled* in weight and had a *nutmeg appearance*:[2]

> *Perhaps the one outstanding gross change in the treated animals was the increased size of the liver, as shown in table 3. In about a fourth of the animals the liver had a "nutmeg" appearance, more frequent on the higher than on the lower dosage levels, and not seen in the controls.*

Likewise, Bennett et al. (1938; part of the so-called Drinker Studies)[18] showed a similar pathological effect with PCBs. The liver weight *doubled* and had a *mottled* appearance:

> *In all animals the livers were enlarged (33 to 90 percent). The average weight increase was 71 percent. They were also friable, pale yellow in color, and somewhat mottled.*

Miller also noted that the primary target organ in PCB-treated rats was the liver (Miller 1944), but he provided no organ weights.[18]

3.5.5. Tissue Analysis

Dr. Eaton suggests that histopathological examinations pre-1970 were not comprehensive. Not true. FDA conducted pathological examinations on the following extensive and comprehensive list of organs in the 1947 DDT study:[2]

> *Paraffin-embedded sections stained with hematoxylin and eosin were routinely made of lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, testis, thyroid and (except in the 200 p.p.m. and control groups) hind leg muscles. Ovary and uterus were sectioned in about half the females, and parathyroids were encountered in about half the thyroid sections. Other structures such as lymph nodes, hind leg bones, and bone marrow, were sectioned in a moderate number of instances, about two dozen of each. Special stains for fat and for iron-containing pigment were done in a few instances.*

Perhaps the most obvious *trigger* for Monsanto that should have prompted it to conduct PCB cancer studies in the 1940s (at minimum) was the finding of greatly increased liver weight together with the *specific* pathological lesions FDA described for DDT.

There is a similar and very striking pattern of liver damage reported in the Drinker studies in 1938 (Bennett et al. 1938) and Miller (1944).[18,19] The FDA study reported that the

histopathological lesions included *hyperplasia* (synonymous with mitotic figures) and *hyalinization:*

> *The characteristic microscopic change in the liver was proportional to dosage level, although the lower grades of the change were generally present even at the lowest dosage level of 200 p.p.m., and in the first series at 100 p.p.m. The lesion consisted principally in hypertrophy and increased cytoplasmic oxyphilia of the centrolobular hepatic cells, plus increased basophilia and margination of the cytoplasmic granules, and a tendency to hyalinization of the remainder of the cytoplasm…Eleven other rats showed varying amounts of nodular adenomatoid hyperplasia; the nodules were generally of 1 to 3 mm. diameter, and were usually noted grossly as scattered yellowish foci.*

Bennett et al. (1938) reported very similar findings for PCB-induced lesions. When they compared rats dosed with penta- and hexachloronaphthalenes, they reported only *an occasional liver* contained hyaline droplets. However, when they dosed another group of rats with the same penta- and hexachloronaphthalenes plus 10% PCBs, they reported the following:[18]

> *Hyaline droplets in the altered cytoplasm were a conspicuous feature (see fig. 3, plate III). Mitotic figures were present in abnormally large numbers.*

Bennett et al. further reported that, although they tested mixtures of chloronaphthalenes and PCBs, there were dramatic increase in the pathological damage and hyalinization when just small amounts of PCBs were added to the mixtures. It is significant that they noted:

> *Feeding of tetra- and pentachloronaphthalenes in combination with chlorinated diphenyl resulted in pronounced liver chances…Microscopic examination revealed a peculiar type of hyaline degeneration involving practically every liver cell (see figs. 1 and 2, plate I). This type of cell degeneration was more marked and occurred earlier after exposure to preparations containing chlorinated diphenyl than to any other compounds tested.* [emphasis added]

Miller (1944) also noted the presence of these *peculiar* round or oval intracellular bodies in rats after 60- and 90-day PCB exposures:[18]

> *In all of the rats receiving 10 such doses peculiar round or oval intracellular bodies were observed in the livers of the animals in both 60- and 90-day groups…These bodies varied considerably in size…It was hyaline and deeply*

> *eosinophilic, with a scant basophilic outer margin, and sometimes presented a concentric lamination. The thickness of this hyaline shell varied.*

Importantly, Miller found that hyalinization was not an acute lesion resulting from a single PCB dose but was only found with repeated exposures—likely due to bioaccumulation:

> *Intracellular hyaline bodies were found in the liver of the rat alone. They were present, usually in large numbers, in all of the rats receiving 10 0.05-cc. doses and in some of the animals receiving 25 doses by skin and corneal applications and ingestion, but were not observed in any of the animals subjected to single doses…None were observed in rats examined prior to 50 days on test.*

Miller also confirmed my opinion that these hyaline bodies were rare. His findings were consistent with those of Bennett et al. (1938) and, therefore, could be used as hallmarks of chlorinated compounds:

> *These findings agree with Bennett [Bennett 1938] who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.*

Miller apparently thought these hyaline figures so unique and specific for PCB-treated rats that he presented a single photomicrograph of these *peculiar* morphological structures in his publication (he showed no other photomicrographs). (See Exhibit 12.)

Exhibit 12. Figure 1 from Miller 1944: Intracellular Hyaline Bodies in the Livers of Rats Exposed to a PCB

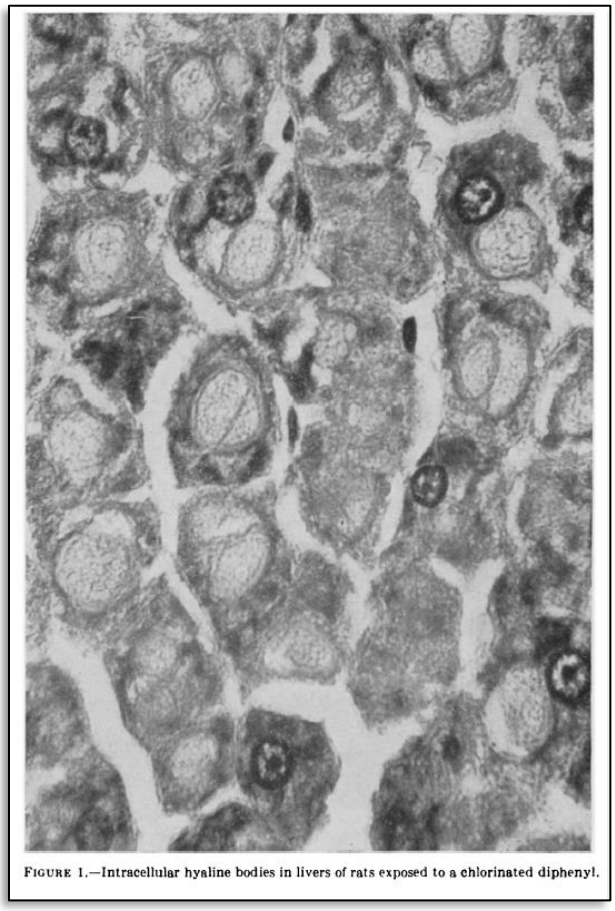


FIGURE 1.—Intracellular hyaline bodies in livers of rats exposed to a chlorinated diphenyl.

Source: Miller 1944.[19]

The similarities between pathological lesions reported in the Drinker PCB studies (Bennett et al. 1938), the Miller study (1944), and the FDA DDT study (Fitzhugh and Nelson 1947) are obvious and unmistakable.[2,18,19] Reading these three studies side-by-side, it is clear that there are many similarities between DDT and PCBs with regard to the specific lesions reported—particularly, the increased liver weight and the unique and peculiar hyaline bodies. The increased liver weight and the presence of hyaline bodies are hallmarks of tumorigenesis. What Drinker and Miller could not know is whether the early pathological lesions they were describing would progress to hyperplastic nodules or tumors that were later described by FDA in the 1947 DDT cancer study. The reason is simply that both Drinker and Miller were conducting subacute studies that were

terminated after only a few months. If they *had* conducted chronic, long-term cancer studies and continued their PCB dosing for the entire 2-year exposure in rats, I have little doubt that they would have found PCBs were carcinogenic even before the FDA showed in 1947 that DDT was carcinogenic.

3.6. Dr. DeGrandchamp Response to Dr. Eaton's Answer to Charge Question 4 (Dr. Eaton Report, Page 86)

Dr. Eaton was asked to consider whether an animal cancer test performed during the 1930s–60s would have shown that PCBs caused cancer in laboratory animals:

> **Charge 4:** *Consider whether, if an animal test for cancer had been performed in the 1930's–60's, it would have demonstrated that PCBs cause cancer in laboratory animals.*
>
> **Dr. Eaton Response:** *Had Monsanto found a laboratory willing and able to conduct a 'test for cancer' in the 1930s, 40s, or 50s, or established its own, it is highly unlikely that the study would have found a statistically significant increase in tumors from PCBs.*

Dr. Eaton states as his rationale:

1. *They likely would have tested the animals for 18 months or less, as was typical of such studies of that time.* (Dr. Eaton Report, page 86.)

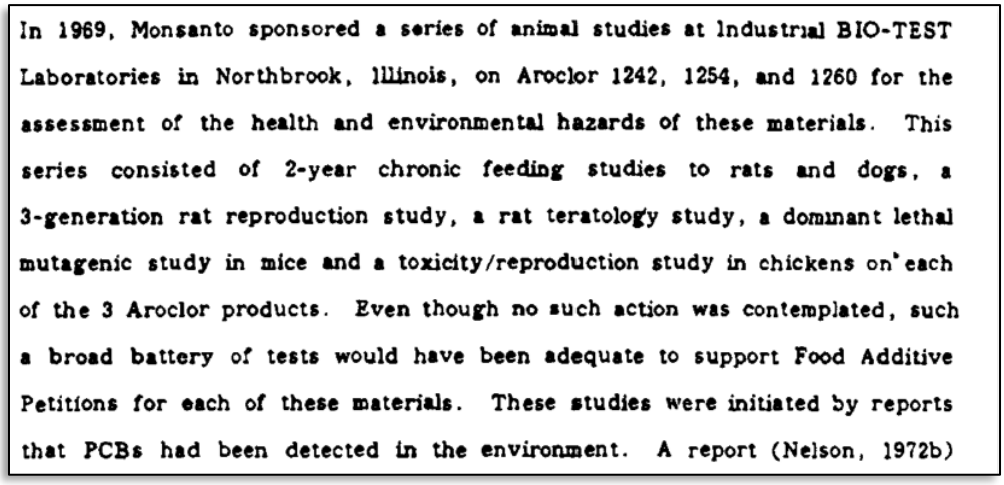
2. *They likely would have used an insufficient dose and/or route of exposure. Nearly all of the toxicology studies done on PCBs in 1930s-1950s were focused on workplace concerns about toxicity following inhalation exposure. The pioneering work of Drs. Drinker and Treon never really considered ingestion as the principle 'route of exposure', although they did do some feeding studies that corroborated the liver as the primary 'target organ' for toxicity of the mixtures of industrial compounds they were studying. Rather, their focus was, appropriately at the time, on workplace exposure via the inhalation route. Had Dr. Drinker or others conducted a 2-year inhalation study of PCBs, it is extraordinarily unlikely that it would have produced an adequate dose to the liver to cause liver tumors, which is the primary form of reproducible, statistically significant tumor develop in rat bioassays of PCB mixtures.* (Dr. Eaton Report, page 86.)

3. *Had Monsanto decided to conduct an inhalation test for cancer, it would likely have used a laboratory such as Dr. Treon's laboratory*. (Dr. Eaton Report, page 87.)

4. *Of 27 different 2-year studies on various commercial mixtures of PCBs (some using only males or females, some using both sexes; see Table 4 on p. 34, see also Appendix 3), only 7 of the 27 studies (26%) identified a positive response for cancers (and two others had increases in benign adenomas)…This rat strain was not widely used prior to the protocol development effort of the Weisburgers in the early 1960s.* (Dr. Eaton Report, page 88.)

It is noteworthy that Dr. Eaton is rationalizing an excuse for why Monsanto did not conduct any 2-year cancer studies until 1969. Furthermore, he is stating that if Monsanto had conducted such studies, it would not have found evidence that PCBs were carcinogens. In all my reviews of the Monsanto memos and documents relating to Monsanto's "toxicity" studies, not one had made a similar excuse. Dr. Eaton's opinion that Monsanto did not conduct any 2-year cancer test because the cancer testing protocols were not standardized is undercut by Monsanto's own statements regarding when—and, more importantly, *why*—Monsanto initiated those very first IBT PCB 2-year cancer tests in 1969 (MONS213386).[17] (See Exhibit 13.)

Exhibit 13. Excerpt from A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls



In 1969, Monsanto sponsored a series of animal studies at Industrial BIO-TEST Laboratories in Northbrook, Illinois, on Aroclor 1242, 1254, and 1260 for the assessment of the health and environmental hazards of these materials. This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice and a toxicity/reproduction study in chickens on each of the 3 Aroclor products. Even though no such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment. A report (Nelson, 1972b)

Source: Levinskas 1981.[17]

This quote is from a lengthy (70-page) Monsanto document: *A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies*, which was authored by Dr. George J. Levinskas in 1981 (MONS213336 to MONS 213405).[17] He states that the only reason Monsanto initiated the IBT studies was because PCB had been detected in the environment.

Dr. Eaton states that Monsanto was not required by any FDA regulatory requirement under the 1938 FD&C law to conduct any toxicity testing. However, Dr. Eaton ignores the fact that Monsanto *did* conduct a broad battery of toxicity tests, including 2-year chronic feeding studies, for Aroclors 1242, 1254, and 1260 for just that purpose. That is, the IBT–Monsanto Aroclor cancer tests were conducted specifically to meet the requirements of the FDA regulation to "support Food Additive Petitions for each of these materials," as stated by Monsanto's Dr. George Levinskas.

This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice, and a toxicity/reproduction study in chickens on each of the three Aroclor products. Even though no

such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment.

As I have discussed, the FDA's 1949 Black Book was written so that the entire chemical industry would have standard protocols that would produce uniform study results. These were intended to provide a testing framework of consistency. They are, in fact, very similar to those toxicological testing protocols Levinskas was referring to in 1969.

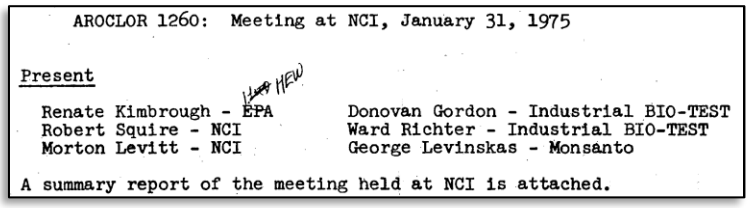
The above statements by Monsanto do not support Dr. Eaton's opinion that the *reason* Monsanto did not conduct 2-year cancer test is that there were no standardized protocols that Monsanto could have followed until 1970. It appears that either Dr. Eaton is *now* claiming that Monsanto did not perform a cancer test on PCBs because the science had not advanced to the point where such tests could be conducted or that, if Monsanto had conducted such tests, it would not have found that PCBs were carcinogenic.

While Dow, DuPont, and Bayer A.G. were testing their chemical products (in the late 1930s) for cancer before they were produced, Monsanto started its cancer testing *after* it had been manufacturing PCBs for 40 years. Simply put, Monsanto started chronic toxicity studies and cancer studies in 1969, and the reason was not because standard scientific protocols for conducting such tests did not exist.

Notwithstanding the fact that standard testing practices were available as early as 1949, Dr. Eaton's discussion of standard practice is *irrelevant* to my opinion. My opinion is that there were at least 50 solid studies that described robust cancer testing methods by 1950. The only issue I address is whether scientific sources of cancer testing information were available and whether a good and robust study design had been developed. If Monsanto had truly been interested in conducting a cancer study in the early 1940s, it needed only to contact the NCI or FDA, both of which employed many cancer experts. Industrial and academic scientists reach out for guidance or to discuss scientific matters on a routine basis. This is just a generally practiced part of scientific collaboration. I have personally contacted many governmental scientists during my approximately 30 years in toxicology practice and have likely had 50 to 100 extensive conversations to acquire knowledge I did not have regarding diverse scientific matters. Even the

Monsanto memos and documents show Monsanto frequently met with governmental officials to discuss *scientific issues*. For example, based on my review of Monsanto memos and documents, Monsanto convened a meeting between U.S. EPA (HEW), NCI, IBT, and Monsanto in 1975 to discuss cancer findings of PCB studies.[20]

Exhibit 14. Excerpt from Aroclor 1260 Meeting at NCI



AROCLOR 1260: Meeting at NCI, January 31, 1975

Present

Renate Kimbrough - EPA (HEW)
Robert Squire - NCI
Morton Levitt - NCI
Donovan Gordon - Industrial BIO-TEST
Ward Richter - Industrial BIO-TEST
George Levinskas - Monsanto

A summary report of the meeting held at NCI is attached.

Source: Levinskas 1975.[20]

Monsanto did not function as a scientific island. It was a major chemical company that could have chosen among hundreds of experts in the cancer testing field. The massive amounts of PCBs Monsanto was producing would have warranted the expenditure of funds for those studies.

In addition to talking to the FDA, Monsanto could have simply adopted the FDA 1949 cancer study for DDT (Fitzhugh and Nelson 1947)[2] and found positive and unmistakable signs of cancer. Dr. Eaton summarizes the state-of-the science without even *citing* (let alone considering) the FDA DDT 1947 study or the 1949 FDA Black Book (Lehman et al. 1949),[2] both of which detail how chronic cancer testing should be conducted. As I previously indicated, the FDA specifically states that its guidance should be used for chemicals that are likely to contaminate foods (based on the massive amounts of PCBs manufactured, this could have been predicted). This is clearly stated in the FDA Black Book Discussion and Summary: [2]

Discussion and Summary

Arnold J. Lehman [Chief, Division of Pharmacology, Food and Drug Administration]

The body of knowledge accumulated as the result of the above described studies has for its purpose the determination of the relative safety of the chemicals proposed for addition to foods or likely to contaminate foods."

Nevertheless, I have been requested to consider Dr. Eaton's rationale for why Monsanto *would not* have found that PCBs were carcinogenic in animal tests. Before addressing each of Dr. Eaton's reasons, it is very important to stress that even the very first study IBT conducted for Monsanto showed PCBs *were* carcinogenic, which the company admitted in numerous documents. This is not my opinion; it is a fact *specifically stated* in *numerous* Monsanto documents. This fact is diametrically opposed to Dr. Eaton's opinion. Despite there being numerous documents stating this fact, none of these Monsanto documents are included in Dr. Eaton's report; Dr. Eaton appears to have chosen to ignore these documents for an unexplained reason. It should also be noted that, after completion of the IBT–Monsanto PCB studies, Monsanto attempted to falsely change IBT's conclusions. Furthermore, Monsanto devised a path forward to outmaneuver other cancer scientists in an attempt to publish IBT's fraudulent and false cancer studies before they could.

The following is a summary of facts regarding Monsanto's own IBT cancer studies, which rebut Dr. Eaton's opinion that those 1971 studies *did not* show PCBs were carcinogenic (when they clearly did):

1. IBT completed the Monsanto 2-year Aroclor cancer tests in 1969. Despite the fact that IBT falsified its reports by replacing dead animals with new animals (among other egregious practices), IBT pathologists still concluded at the end of the study that PCBs *were carcinogenic*.

2. While IBT, CDC, and NCI scientists all concluded Aroclors were carcinogenic, Monsanto argued that PCBs did not cause "malignant" tumors, so they were not carcinogenic. Dr. Eaton is relying on the same discredited and false definition of carcinogenic compounds in his opinion.

3. Monsanto directed IBT to falsify conclusions about whether Aroclors were carcinogenic and to change the cancer classification of PCBs.

Brief descriptions of each of the above issues are in the following sections.

3.6.1. IBT's PCB Studies Proved Aroclors Were Carcinogenic

After IBT completed the Aroclor cancer studies in early 1970, the CDC's Dr. Renate Kimbrough had also just completed an independent cancer study showing that Aroclor 1260 was carcinogenic. IBT decided to review her study and compare her results with its own Aroclor 1260 cancer study. IBT issued a report on the comparison titled, *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458); IBT concurred that Aroclors were carcinogenic.[21]

Monsanto states that Dr. Kimbrough's histopathological examination showed that 170/180 rats developed neoplastic "nodules" and "hepatocellular carcinomas:"

> *It was therefore concluded that Aroclor 1260 has a hepatocarcinogenic effect in female Sherman strain rats.*

The Monsanto document goes on to state that IBT's own pathologist Dr. Gordon came to the same conclusion:

> *Another study in albino rats with Aroclor also showed inconclusive results; while no carcinogenic response could be observed in a preliminary study, Dr. Gordon (Bio-Test Laboratories Inc.) reported a slight tumorigenic property of Aroclor 1242, 1254, and 1260 in rats were fed continuously at levels of 100 ppm for 2 years.*

Exhibit 15 presents the number of carcinogenic lesions in PCB-treated rats versus control rats from the IBT Aroclor 1260 reevaluation study. IBT confirmed that Aroclor 1260 was carcinogenic, with results similar to those of the Dr. Kimbrough's CDC study (the comparative study prompting IBT's reevaluation). The IBT pathologist reported that 179/184 rats developed evidence of carcinogenicity (hyperplastic nodules), which was very similar to Dr. Kimbrough's tally of 170/180 rats showing the same pathology. Despite these very high rates of

carcinogenicity in both the IBT and Kimbrough studies—and the admission by the IBT pathologist who examined the tissues that PCBs were carcinogenic—Dr. Eaton claims the IBT studies *did not* show evidence of cancer.

Exhibit 15. Table 21 from Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260

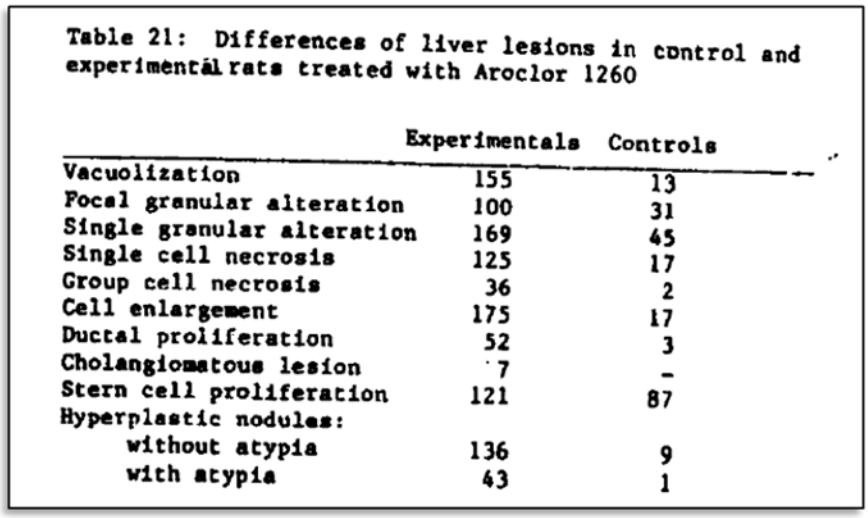


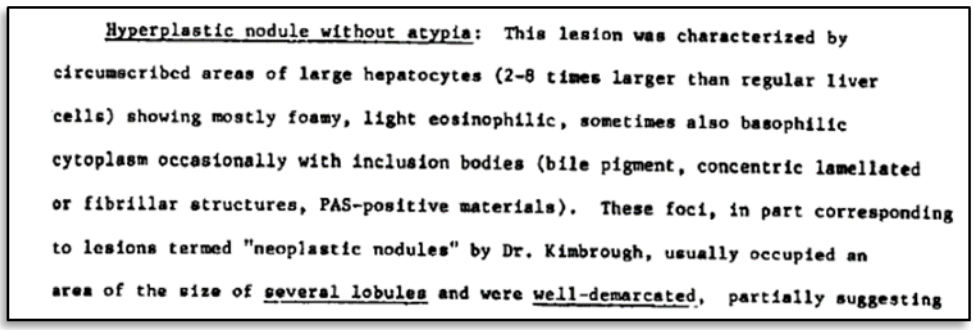
Table 21: Differences of liver lesions in control and experimental rats treated with Aroclor 1260

	Experimentals	Controls
Vacuolization	155	13
Focal granular alteration	100	31
Single granular alteration	169	45
Single cell necrosis	125	17
Group cell necrosis	36	2
Cell enlargement	175	17
Ductal proliferation	52	3
Cholangiomatous lesion	7	-
Stern cell proliferation	121	87
Hyperplastic nodules:		
without atypia	136	9
with atypia	43	1

Source: *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458).[21]

I have previously discussed hyaline bodies or inclusions as unique pathological features that should have been seen by Monsanto as triggers that prompted the company to conduct cancer studies in the 1930s or 1940s because they were reported as important PCB-induced lesions by both Drinker (1938) and Miller (1944).[19,22] Hyaline bodies were also described in the FDA DDT cancer study (Fitzhugh and Nelson 1947) as developing during tumorigenesis.[2] The relevance and importance of these pathological features is that they were also described by Monsanto as being among the prominent pathological lesions in its cancer studies (Exhibit 16). IBT reports that the hyperplastic nodules contained "inclusion bodies" with "lamellated PAS-positive materials" (which is synonymous with hyaline bodies).

Exhibit 16. Excerpt from Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260



Hyperplastic nodule without atypia: This lesion was characterized by circumscribed areas of large hepatocytes (2-8 times larger than regular liver cells) showing mostly foamy, light eosinophilic, sometimes also basophilic cytoplasm occasionally with inclusion bodies (bile pigment, concentric lamellated or fibrillar structures, PAS-positive materials). These foci, in part corresponding to lesions termed "neoplastic nodules" by Dr. Kimbrough, usually occupied an area of the size of several lobules and were well-demarcated, partially suggesting

Source: *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458).[21]

3.6.2. While IBT, CDC, and NCI Scientists All Concluded Aroclors Were Carcinogenic, Monsanto Argued that PCBs Did Not Cause "Malignant" Tumors, So They Were Not Carcinogenic

IBT, CDC, and NCI all agreed that the correct classification of a carcinogen is based on both benign and malignant pathological evidence. Monsanto asserted that PCBs should not be classified as carcinogens because they did not produce malignant tumors that metastasized (malignant tumors were never the definition of carcinogenicity). Dr. Eaton is relying on the same discredited histopathological criteria that Monsanto claimed in the 1970s, only to be corrected by the NCI consensus statements presented in Report of a Workshop on Classification of Specific Hepatocellular Lesions in Rats (Squire and Levitt, 1975).[23] The workshop, consisting of 20 experts in pathology and experimental carcinogenesis met for 2 days (December 11–13, 1974) to establish standardized terminology and criteria to identify tumorigenic pathological lesions. The NCI's role in such standardization was clearly defined:

> *The Carcinogenesis Bioassay Program of the National Cancer Institute has broad responsibility for detecting environmental carcinogens and depends upon the evaluation of specific tumor diagnoses by the National Cancer Institute and collaborating scientists throughout the country. Of prime importance in many of the results is the interpretation of proliferative lesions of rodent livers. It is vital*

to the goals of the Program that these lesions are properly classified and a nomenclature agreed upon.

Squire and Levitt summarized the participants' consensus pathological criteria and nomenclature in Exhibit 17. It is noteworthy that this was the same classification scheme used by CDC, NCI, and IBT in their pathological evaluation of the PCB cancer studies in which the "Foci of cellular alteration" were included as important criteria. That is, both Dr. Kimbrough and IBT identified carcinogenic changes in Aroclor-treated animals consistent with the recommended classification scheme shown below. Monsanto disagreed with Dr. Kimbrough and its own consultant (IBT).

Exhibit 17. Table 1 from Squire and Levitt: Classification of Hepatocellular Lesions in Rats

Table 1

Recommended classification of specific hepatocellular lesions in rats

I.	Foci of cellular alteration
	A. Clear cell foci
	B. Eosinophilic or ground glass foci
	C. Basophilic foci
	D. Mixed cell foci
II.	Neoplastic nodules
III.	Hepatocellular carcinomas
	A. Well differentiated
	B. Moderately differentiated
	C. Poorly differentiated
	D. With glandular and/or papillary formation
IV.	Cholangiofibrosis

Source: Squire and Levitt 1975.[23]

Contrary to Monsanto's discredited classification scheme, in which clear evidence of tumor malignancy was necessary, the NCI stated that foci of cellular alteration (which are not evidence of malignancy or metastasis) are important criteria because they may be a part of the "spectrum capable of processing to the formation of nodules." This specific rational succinctly stated by NCI is the same criteria I applied and relied on to conclude that, based on my evaluation of the Drinker (Bennett et al. 1938) and Miller (1944) studies, the lesions were consistent with the same lesions the NCI explained to be the spectrum of histological changes that could proceed to nodules and then into tumors.[18,19] Drinker and Miller identified the early pathological hallmarks

that could represent tumorigenesis (as stated by NCI). I did not opine that I was certain they would process into tumors. Because they were the characteristic hallmarks of cancer that are seen in the early stage (that were well-known at the time), the presence of these lesions should have been a trigger for Monsanto to confirm or negate that PCBs were carcinogenic. Drinker and Miller could not have known that PCBs were carcinogenic at the time because both experiments lasted only about 3 months. However, the IBT PCB cancer studies and most of the other cancer studies did confirm that the early hallmarks I described in my expert report were consistent with the NCI classification of early tumor formation. That is, they were part of the spectrum that progressively (with continued PCB exposures) leads to carcinogenic effects. Dr. Eaton states that my opinion is incorrect, despite the fact that all cancers develop gradually during tumorigenesis. Cancer does not simply suddenly appear overnight.

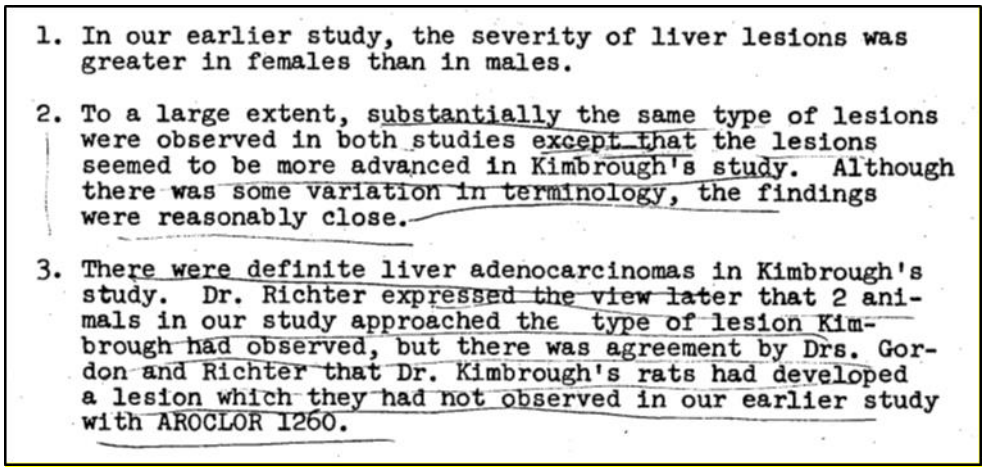
As noted, the NCI classification workshop developed *consensus* among all cancer experts (which is often rare) regarding the appropriate pathological criteria and nomenclature to describe the pathological manifestation of carcinogenesis. Despite the scientific consensus of the leading cancer researchers of the time, Monsanto continued to disagree with the NCI classification scheme because no actual *malignant tumors* were detected in the PCB cancer studies.

Because the NCI pathological classification scheme would obviously have major ramifications for considering Monsanto's Aroclors safe and nontoxic if they were classified as carcinogens, Monsanto convened a scientific meeting between CDC (Dr. Kimbrough), NCI, IBT (Dr. Gordon, Section Head, Pathology), cancer experts, and Dr. Levinskas from Monsanto on January 31, 1975, to discuss the classification scheme and to also allow the experts from all three groups to microscopically review the rat liver tissues from PCB-treated animals.[20] Dr. Kimbrough and IBT had completed their cancer studies of Aroclor 1260, and extensive pathological examinations were conducted for the two studies. The goal was two-fold. The first was to reach consensus among the experts that the NCI classification was being appropriately applied to PCB-treated rat livers. The second was to make a side-by-side *comparison* between the Dr. Kimbrough and IBT study microscope slides to determine if the CDC and IBT pathologies were the same.

Dr. Levinskas also wrote a summary memo (STLCOPCB4052173) for the meeting attendies (CDC, NCI, IBT, and Dr. Levinskas) that captured the scientific discussion and conclusions

based on the actual microscopic histopathological examination of the type and quantity of carcinogenic lesions in Aroclor 1260 rat livers from the CDC and IBT studies, on which they reached consensus. More importantly, however, was the side-by-side examination of CDC and IBT rat liver histology studies. According to Monsanto's own notes, CDC, NCI, and IBT pathologists all agreed that the CDC and IBT study results were essentially the same. Monsanto's Dr. Levinskas summarized his conclusions, making the three important points, as presented in Exhibit 18.

Exhibit 18. Excerpt from Aroclor 1260: Meeting at NCI, January 31, 1975



1. In our earlier study, the severity of liver lesions was greater in females than in males.

2. To a large extent, substantially the same type of lesions were observed in both studies except that the lesions seemed to be more advanced in Kimbrough's study. Although there was some variation in terminology, the findings were reasonably close.

3. There were definite liver adenocarcinomas in Kimbrough's study. Dr. Richter expressed the view later that 2 animals in our study approached the type of lesion Kimbrough had observed, but there was agreement by Drs. Gordon and Richter that Dr. Kimbrough's rats had developed a lesion which they had not observed in our earlier study with AROCLOR 1260.

Source: Levinskas 1975.[20]

Dr. Levinksas's summary memo (STLCOPCB4052173) was sent to all attending meeting experts, and they were invited to respond to Dr. Levinskas if they felt his memo incorrectly summarized the scientific consensus of the meeting.

Despite, what appears to be a straightforward summary of the meeting sent to the attendees, however, Dr. Levinksas wrote another internal summary memo for Monsanto management that makes it clear Monsanto was not pleased with the outcome.[20] Dr. Levinskas was clearly hoping that there would be a different conclusion, given that IBT's pathologist attended the meeting. That hope was dashed because the IBT pathologist concurred with CDC and NCI experts, with all concluding that Aroclor 1260 was a carcinogen. Furthermore, in discussing Dr. Kimbrough's

Aroclor 1260 findings that showed it was a carcinogen in her study, Dr. Levinskas himself had to conclude that her results were hard to refute. He came to this conclusion even though Dr. Kimbrough did not have any data on "spontaneous tumor rates" in untreated rats from her study.

> *Control animals in this study had very "clean" livers. The incidence of spontaneous changes was quite low. Insofar as could be determined, Dr. Kimbrough has no data from other 2-year studies which could be used to assess the spontaneous tumor incidence of this strain of rat. Despite the absence of historical control date, her results would be hard to refute.*

Dr. Levinskas's statement is important for two reasons. First, Monsanto concluded that Dr. Kimbrough's study and conclusions were scientifically valid because it presented overwhelming evidence of PCB-induced carcinogenicity. Second, Monsanto's acceptance of Dr. Kimbrough's results indicates that Dr. Eaton is not correct in stating that a laboratory must have historical evidence of spontaneous tumor rates and that this was a standard practice post-1970, as he states in Table 12 from his report.

In the internal memo, Dr. Levinskas (Monsanto) goes on to state that he was only an observer and he was unable to "caucus" with IBT's pathologist during the meeting with Dr. Gordon. Dr. Levinskas states:

> *After we left, and they* [presumably, IBT's Dr. Gordon] *conceded to the occurrence of hepatic carcinomas, there was little else to do. I got the impression that Dr. Kimbrough plans early publication of her findings.* [emphasis added]

Failing in the effort to alter, modify, or change the conclusions of CDC, NCI, or IBT based on the actual scientific findings and merits of the reexamination of the rat liver tissue, Monsanto had little recourse. Consequently, Dr. Levinska's plan on how to proceded was to:

> *…publish our 2-year study on AROCLOR 1260 before Dr. Kimbrough gets into print. This would at least blunt the impact of her study.*

It is not clear from Dr. Eaton's report that he has reviewed these Monsantos memos or if they were part of his reliance materials. However, it is clear that by 1975, the IBT cancer studies were consistent with other independent cancer studies in proving Aroclors were carcinogenic.

Based on all of the above facts and information, Dr. Eaton's Table 4 is incorrect, and his conclusions regarding Aroclor-induced cancer in laboratory animals is not credible. I show part of his Table 4, which is incorrect for two reasons. First he shows that Monsanto's own IBT studies were not positive for cancer, I have disputed that a thorough review of both IBT's *Histopathological Re-evalutation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS043458) and Dr. Levinskas own admission that CDC, NCI, as well as IBT's pathologist reached consensus Aroclor 1260 was carcinogenic. This part of his table is incorrect. Secondly, Dr. Eaton's table while correctly showing that the Kimbrough study was positive for cancer the IBT studies were negative even though Dr. Levinskas admitted that the consensus amoung CDC, NCI, and IBT experts was that Dr. Kimbrough's and IBTs study results were "subsantially the same." If the studies were substantially the same it would not be possible to have one study negative for cancer while the other is positive.

Exhibit 19. Table 4 from Dr. Eaton Report: Summary of 2-Year Carcinogenicity Bioassays Completed on Commercial Mixtures of PCBs, 1971, 1972, 1974, and 1975

Table 4. Summary of 2-year carcinogenicity bioassays completed on commercial mixtures of PCBs

Year	Species and strain	Test group numbers	Dose groups (ppm)	PCBs studied	Positive for cancer (M, F)*	Reference
1971	CR Albino rats; males and females	8 groups; 50 per group	0, 1, 10, 100	Aroclor 1242 Aroclor 1254 Aroclor 1260	No, No No, No No, No	(IBT, 1971a) (IBT, 1971b) (IBT, 1971c)
1972	Dd mice	4 groups; 6-12 per group	0, 100, 250, 500	Kanechlor 300 Kanechlor 400 Kanechlor 500	No No Yes	(Nagasaki *et al.*, 1972) (Ito *et al.*, 1973a; Ito *et al.*, 1973b)
1974	Male Wistar rats	4 groups, 10-25 per group; fed for 1 yr	0, 100, 500, 1000	Kanechlor 300 Kanechlor 400 Kanechlor 500	No No No	(Ito *et al.*, 1974)
1975	Female Sherman rats	2 groups, 200 per group	0, 100	Aroclor 1260	Yes	(Kimbrough *et al.*, 1975)

Source: Eaton 2019.[4]

3.6.3. Monsanto Directed IBT to Falsify Conclusions about Whether Aroclors Were Carcinogenic and to Change the Cancer Classification of PCBs

By 1975, consensus was reached between CDC, NCI, and IBT pathologists that Aroclors were carcinogenic in long-term animal studies (STLCOPCB4052174). Despite this development, Monsanto continued to pressure IBT to misrepresent the conclusions. As I discussed in my expert report (page 69), despite IBT's stated results and conclusions that Aroclors were carcinogenic, Monsanto continued to coerce and force IBT to change the cancer classification for Aroclors.

In addition to the evidence I have already discussed in my expert report, the document presented in Exhibit 20 through 0 should also be considered evidence of Monsanto's efforts to mislead CDC and NCI scientists about the carcinogenicity of Aroclor 1260, as it is relevant to the above facts and discussion. This document is a cover letter from Dr. Calandra (President of IBT) to Dr. Levinskas (Monsanto) that was attached to the IBT report: *Two-year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections*, March 24, 1975.[24] This document is important for four reasons:

1. The date it was sent;

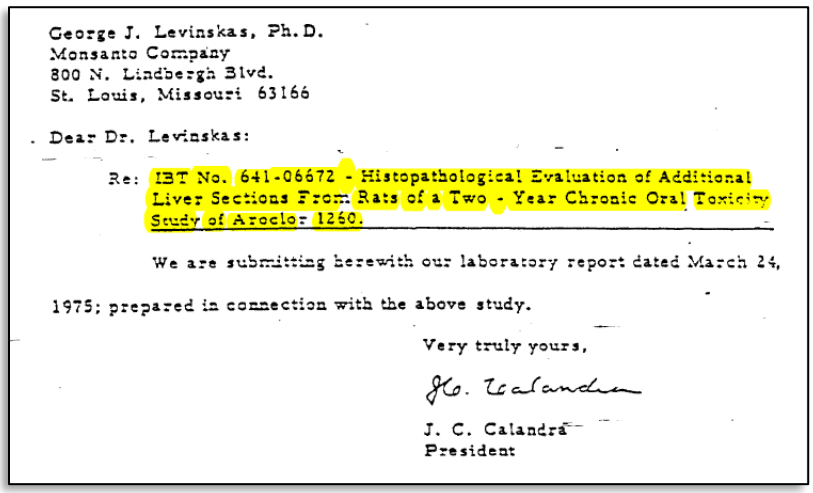
2. Who it was sent to at Monsanto;

3. Who signed the report; and

4. That the carcinogenic classification was deliberately and falsely changed from "slightly carcinogenic" to noncarcinogenic.

While I discussed the letter sent by Monsanto forcing IBT to change the classification in my expert report, I have since reviewed the sequence of scientific meetings that preceded that letter. First, this cover letter with attached report was dated March 24, 1975, which was approximately 2 months *after* the January 31, 1975, expert meeting convened by Dr. Levinskas (Monsanto) with CDC (Dr. Kimbrough) and NCI experts, and IBT pathologist Dr. Gordon in which all experts concurred, along with Dr. Levinskas (Monsanto) that Aroclor 1260 was carcinogenic.

Exhibit 20. Cover page from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1260.

We are submitting herewith our laboratory report dated March 24, 1975; prepared in connection with the above study.

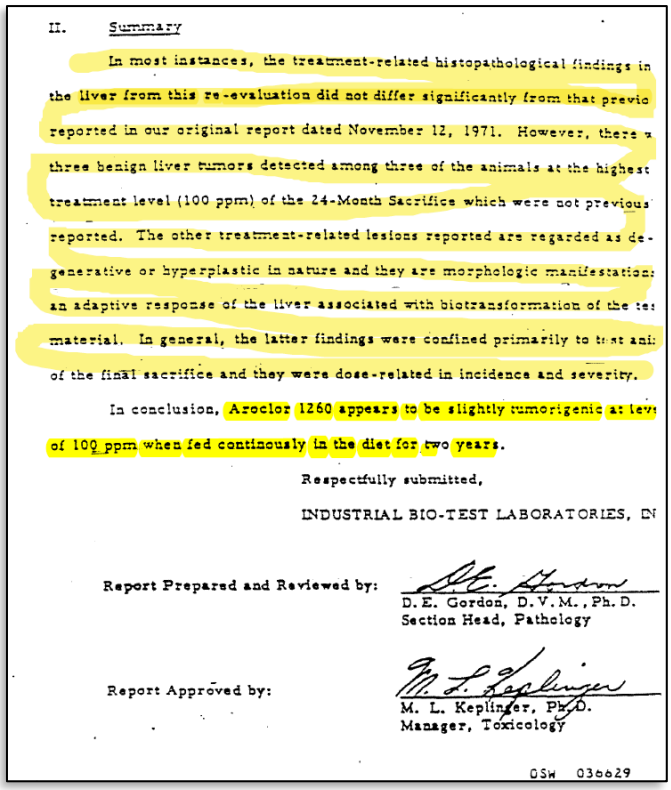
Very truly yours,

J. C. Calandra
President

Source: Calandra 1975.[24]

The summary of the report indicates that a reexamination of the PBC rat liver tissues showed Aroclor 1260 was *slightly tumorigenic*. This document was signed by IBT's Dr. Gordon and sent to Dr. Levinskas.

Exhibit 21. March 24, 1975, Summary from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



II. Summary

In most instances, the treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previo reported in our original report dated November 12, 1971. However, there w three benign liver tumors detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previous reported. The other treatment-related lesions reported are regarded as de- generative or hyperplastic in nature and they are morphologic manifestation an adaptive response of the liver associated with biotransformation of the te material. In general, the latter findings were confined primarily to test ani of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 appears to be slightly tumorigenic at lev of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, IN

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph. D.
Manager, Toxicology

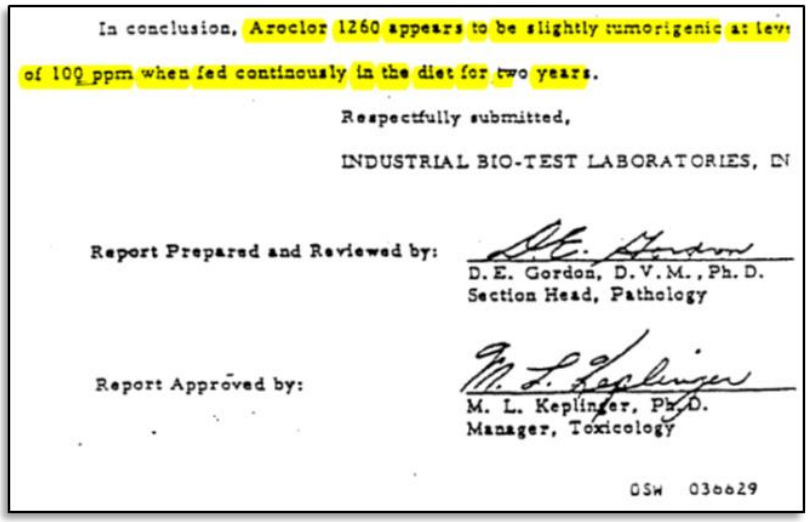
OSW 036629

Source: Calandra 1975.[24]

However, another document was prepared that stated Aroclor 1260 was *not* carcinogenic. Both documents are signed by Dr. Gordon (with what appears to be the identical signature).[24] Since this document was sent approximately 2 months after CDC, NCI, and IBT (Dr. Gordon) reached consensus that Aroclor 1260 was carcinogenic, Dr. Gordon knew in March, 1975, that this conclusion was false. He intentionally produced this document to mislead governmental

scientists; obviously Dr. Levinskas knew that as well, since he organized and participated in the March 1975 meeting.

Exhibit 22. March 24, 1975, Conclusion from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



In conclusion, Aroclor 1260 appears to be slightly tumorigenic at leve
of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, IN

Report Prepared and Reviewed by:

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

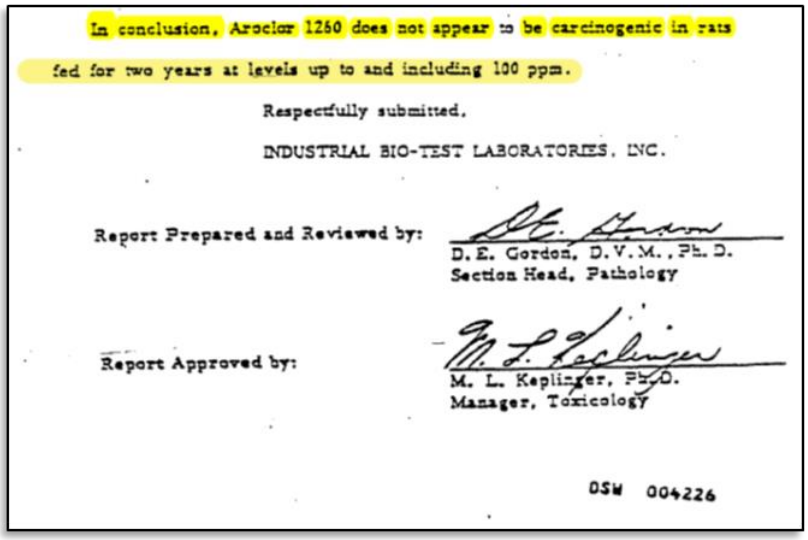
Report Approved by:

M. L. Keplinger, Ph.D.
Manager, Toxicology

OSW 030629

Source: Calandra 1975.[24]

Exhibit 23. Final Page from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



In conclusion, Aroclor 1260 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by:

M. L. Kaplinger, Ph.D.
Manager, Toxicology

OSW 004226

Source: Calandra 1975.[24]

Dr. Levinskas also noted in his review compendium (MONS213337) that the BIO-TEST Laboratories had been challenged and that an evaluation of experimental protocol and data from the Aroclor 1242, 1254, and 1260 IBT studies were carried out, revealing significant discrepancies.[17] He noted specifically that "The review showed that the data bases (including a lack of protocol) were insufficient for a complete validation of the study."

> *Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a, b, c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals.*

> *Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers.*

This statement by Monsanto also undercuts Dr. Eaton's claim that post-1970, testing protocols were standard practice. As stated in Monsanto's own document, the IBT studies did not even have a formal experimental protocol.

On Page 86 of Dr. Eaton's expert report, he lists four reasons for the following statement:

> *Had Monsanto found a laboratory willing and able to conduct a 'test for cancer' in the 1930s, '40s, or 50s, or established its own, it is highly unlikely that the study would have found a statistically significant increase in tumors from PCBs.*

The following sections rebut his opinions.

3.6.4. ***Dr. Eaton Point 1: They Likely Would Have Tested the Animals for 18 Months or Less, as Was Typical of Such Studies of that Time (page 86)***

Dr. Eaton's term *typical* is not defined, and he does not discuss how he concluded that the more than 1,000 cancer studies that were published by the end of 1949 "typically" only lasted 18 months or less. This is a completely unsubstantiated statement and is in contrast to my opinion that most robust cancer studies were chronic dosing studies lasting a full 2 years or longer. However, if the studies he is referring to are studies in which tumors were found by 18 months, then it would be perfectly correct to terminate the study because it would have been successful. That is, the sole purpose of a cancer test is to determine if a chemical is a carcinogen; when tumors are identified prior to 2 years, it would be a waste of funds to continue the study.

Dr. Eaton is again misrepresenting the standard accepted practice of toxicology and constructing a false framework about whether Monsanto *could* have and *should* have proceeded with developing a cancer testing protocol for PCBs. It is not clear why Dr. Eaton continues to focus on typical practices in the 1930s–1960s when he has, in fact, not actually provided any evidence of what typical means—but that is irrelevant to this case. There was a very easy, cost-effective, and scientifically tenable cancer testing protocol that Monsanto could have developed that would

have had the added benefit of the imprimatur of governmental approval if Monsanto had simply chosen to follow the FDA standard protocol for testing DDT that was published in 1947.[2] This would have been easy because Monsanto would not have had to review the methods from more than 1,000 published studies, cost-effective because it would spend no time with pilot studies, and scientifically tenable because it was proven to be a good method for identifying carcinogens because the FDA had already used it to classify DDT as a carcinogen.

Dr. Eaton is also incorrect that studies were *typically* tested in chronic studies for *18 months or less.* This is easily disproven. The 1949 FDA Black Book clearly states that *all chronic rat studies are 2-year lifetime studies* (this alone proves Dr. Eaton's statement regarding what was typical is irrelevant).[1]

3.6.5. Dr. Eaton Point 2: They Likely Would Have Used an Insufficient Dose and/or Route of Exposure. Nearly All of the Toxicology Studies Done on PCBs in 1930s–1950s Were Focused on Workplace Concerns about Toxicity Following Inhalation Exposure (Page 86)

This statement is incorrect for numerous reasons. Most importantly, he mischaracterizes the routes of exposure in early PCB studies:

- Dr. Drinker's study specifically did include ingestion, despite the fact that his study was a "cause of death study" in the workplace;[22] and

- Dr. Miller's study, which is the best and most comprehensive PCB toxicology study that was published before the 1970s is not even cited in Dr. Eaton's supporting rationale. Dr. Miller also included the route of ingestion in his study design.[19]

Furthermore, the studies that Monsanto should have been using include the following:

- The FDA Black Book 1949 was specifically prepared for the chemical industry to standardize testing methods for chemicals that could contaminate food, which solely focused on contaminant ingestion.

- The FDA DDT 1947 study was only based on ingestion.[2]

Dr. Eaton's following statement highlights the major problem I have addressed in my expert report:

> *Nearly all of the toxicology studies done on PCBs in 1930s-1950s were focused on workplace concerns about toxicity following inhalation exposure.*

This is not factually correct. Nevertheless, it is telling because it points out that Dr. Eaton's concern is that exposures in the workplace should have been the foremost concern for Monsanto, not the general public exposed to PCBs.

3.6.6. Dr. Eaton Point 3: Had Monsanto Decided to Conduct an Inhalation Test for Cancer, It Would Likely Have Used a Laboratory Such as Dr. Treon's Laboratory (page 87)

Dr. Eaton's comment is baseless and without merit. First, Dr. Treon was not an expert in cancer. Second, there were excellent academic, industrial, and governmental cancer testing laboratories. Third, I have reviewed the "Treon studies," and my opinion is that they are some of the worst-designed toxicity studies I have ever reviewed, and I have likely reviewed about 2000 studies in my toxicology practice. The Treon studies provide little relevant information about the toxicity of PCBs.

While Dr. Eaton relies on the Treon studies for his opinion, it is not credible for a scientist to use a single animal and conclude anything from that result, which the Treon study does. In fact, Dr. Eaton highlights the fact that the Treon studies used ridiculously few animals, but states that Monsanto would likely have given the task of conducting cancer studies to that laboratory (which is illogical). It is noteworthy that one of Dr. Eaton's opinions is that many of the pre-1970 early cancer studies did not use enough animals, but he is relying on the Treon study that used a single animal or two cats.

3.6.7. Dr. Eaton Point 4: Of 27 Different 2-Year Studies on Various Commercial Mixtures of PCBs (Some Using Only Males or Females, Some Using Both Sexes; See Table 4 on p. 34, See Also Appendix 3), Only 7 of the 27 Studies (26%) Identified a Positive Response for Cancers (and Two Others Had Increases in Benign Adenomas)… There Are Also Obvious Strain Differences in Rats, with Female Sprague Dawley Rats Showing, by Far, the Most Sensitive Response. This Rat Strain Was Not Widely Used Prior to the Protocol Development Effort of the Weisburgers in the Early 1960s.

Dr. Eaton is incorrect that only 7 of the 27 studies showed signs of cancer. The number of studies he states showed cancer is based on a misstatement of the pathological criteria for identifying evidence of carcinogenesis, as I have discussed. I provided the U.S. EPA summary of cancer tests performed that they considered relevant and pertinent to their classification. Both benign and malignant tumors were considered evidence of carcinogenicity based on the December 1974 NCI workshop (Squire and Levitt 1974). [23] The introduction states that the purpose was to classify the histopathology evidence of carcinogens:

> *On December 11 to 13, 1974, The National Cancer Institute sponsored a workshop in Silver Spring, Md. on the classification of hepatocellular tumors and related lesions of rats. There were 20 participants with extensive and varied experience in pathology and experimental carcinogenesis.*

It is the responsibility of the NCI to establish clear standards and guidelines for carcinogens, as stated in the report:

> *The Carcinogenesis Bioassay Program of the National Cancer Institute has broad responsibility for detecting environmental carcinogens and depends upon the evaluation of specific tumor diagnoses by the National Cancer Institute and collaborating scientists throughout the country. Of prime importance in many of the results is the interpretation of proliferative lesions of rodent livers. It is vital to the goals of the Program that these lesions are properly classified and a nomenclature agreed upon.*

Dr. Eaton appears to be imposing his own ad hoc criteria for pathological carcinogenicity that are contrary to, and fall well short of, the 1975 NCI classification presented previously (Exhibit 17).

Neoplastic nodules, which are considered the insipient stage leading to cancer, were defined as evidence of carcinogenicity. NCI states:

> *The nature of these lesions is controversial. Nevertheless, several participants felt that the basophilic foci or areas had greater significance with respect to tumor development than did the other cellular alterations. Most participants agreed that foci or areas were cytologically similar to the cellular elements of neoplastic nodules and may be part of the spectrum capable of progressing to the formation of nodules.*

In Dr. Eaton's opinion, foci of cellular alterations, which were clearly identified as carcinogenic evidence, were disregarded. The NCI's statement simply means that benign early evidence of hyperplastic changes are in themselves evidence of a carcinogen.

According to the U.S. EPA:

> *Of the 3 studies with PCBs having an average chlorine content of 60%, one reported hepatocellular carcinomas (Kimbrough, et al. 1975) and 2 did not (Levinskas, 1981 and Weltman and Norback, 1978). Since Kimbrough, et al (1975) and Levinskas (1981) both used Lot No AK-3 of Aroclor 1260, the different conclusions they reached are not related to differences in the text material. In addition to the use of a different strain of rat, Kimbrough, et al. (1975) used a different histologic diagnostic criteria. Kimbrough, et al. (1975) used the criteria for classification of specific hepatocellular lesions in rats developed at a National Cancer Institute Workshop (Squire and Levitt, 1975). That workshop recommended that the term "neoplastic nodules" replace so-called "hyperplastic nodules" because "Such nodules are proliferative lesions*…(PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures 1996)

3.7. Dr. Eaton Is Incorrect with Regard to the Number of Animal Cancer Studies Positive for Carcinogenicity

1. Dr. Eaton is incorrect that only 7 of the 27 studies showed signs of cancer. The number of studies he states showed cancer are based on a misstatement of the pathological criteria for identifying evidence of carcinogenesis as I have discussed. I provided the U.S. EPA summary of cancer tests performed that they considered relevant and pertinent to their classification. Both benign and malignant tumors were considered evidence of carcinogenicity based on the December 1974 NCI workshop: Report of a Workshop on Classification of

Specific Hepatocellular lesions in Rats (Squire and Levitt 1974) as I have discussed.

2. Dr. Eaton states that Sprague Dawley are particularly responsive to PCBs and that they were not widely available until 1960. The fact is that Sprague Dawley breed was one of the first colonized strain created by R. W. Dawley in 1925 (available at: https://www.janvier-labs.com/rodent-research-models-services/research-models/per-species/outbred-rats/product/sprague-dawley.html) so clearly they could have been used as early as the 1930's. However, Dr. Eaton ignores the fact that the

3. Dr. Eaton is incorrect by stating that the Sprague Dawley rat is the most sensitive and would not have been used in early PCB cancer studies. The fact is, the very first PCB cancer studies I discussed previously showed that neither the Kimbrough study nor the IBT studies used Sprague Dawley rats and the number of rats in Dr. Kimbrough's study showing carcinogenic lesions was 170/180 and this was closely matched the IBT study in which 179/184 had similar lesions (as was confirmed by IBT and Monsanto). While Dr. Kimbrough used the Sherman strain of rat, IBT used the Charles River CD strain both studied found that more than 90% of the rats showed pathologic carcinogenic lesions.

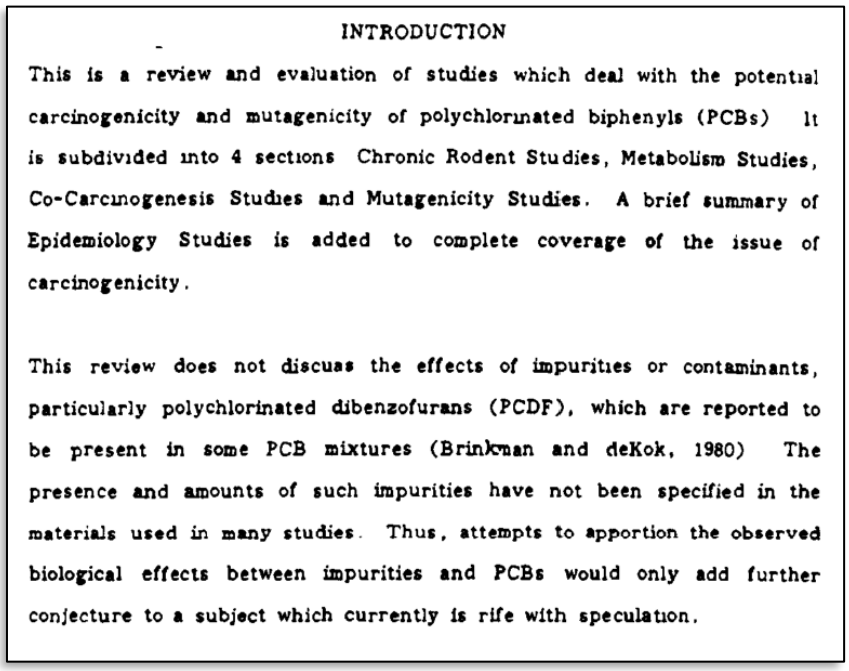
4. Dr. Eaton's opinion is based on an easily disproven incorrect assumption simply based on the high rate of animals that developed cancer in which the test animal was not a Sprague Dawley rat.

5. While Dr. Eaton is correct in concluding that not all PCB cancer studies show the same result with the exact number of animals showing carcinogenic effects, this is not a surprising result to most toxicologists. Indeed, it is to be expected. Although most toxicologists would agree that cigarette smoking causes cancer, not everyone who does smoke will develop cancer. This (expected) finding does not prove cigarette smoke is not a carcinogen (although the cigarette industry attempted to use the same argument decades ago). This is essentially the argument suggested by Dr. Eaton.

6. While Dr. Eaton suggests the reason Monsanto would not have found cancer in Pre-1970 is due to the fact that not many laboratories were not using Sprague Dawley rats in their cancer study he does not discuss or even broach the more plausible reason not all PCB cancer studies show the same result. And this reason is that Aroclors contained contain varying amounts of a very

toxic and carcinogenic group of impurities or contaminants called polychlorinated dibenzofurans (PCDF). This issue is not discussed by Dr. Eaton but it is a well-known fact among academic and regulatory scientists, governmental agencies and Monsanto scientists. For example, Monsanto's Dr. Levinskas prepared a lengthy (70 page) compendium describing the state-of-the-science discussing PCB toxicity in 1981: *A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls* (MON213337) in which he admits that PCDF were contaminants in Aroclors in his introductory section, stating:

Exhibit 24. Introduction from A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies Biphenyls



INTRODUCTION

This is a review and evaluation of studies which deal with the potential carcinogenicity and mutagenicity of polychlorinated biphenyls (PCBs) It is subdivided into 4 sections Chronic Rodent Studies, Metabolism Studies, Co-Carcinogenesis Studies and Mutagenicity Studies. A brief summary of Epidemiology Studies is added to complete coverage of the issue of carcinogenicity.

This review does not discuss the effects of impurities or contaminants, particularly polychlorinated dibenzofurans (PCDF), which are reported to be present in some PCB mixtures (Brinkman and deKok, 1980) The presence and amounts of such impurities have not been specified in the materials used in many studies. Thus, attempts to apportion the observed biological effects between impurities and PCBs would only add further conjecture to a subject which currently is rife with speculation.

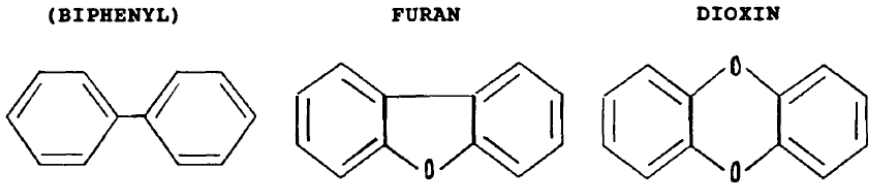
Source: Levinskas 1981.[17]

7. I am also well familiar with this issue because I was a toxicological consultant to the U.S. Department of the Navy, Environmental Health Center, Bureau of Medicine and Surgery for many years investigating PCB polluted Naval Installations sites, conducting toxicological/risk assessments, and training physicians and environmental scientists. As part of my training materials, I used numerous Navy studies and guidance manuals, including: *Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzofurans (PCDFs),*

and Polychlorinated Dioxins (PCDDs) (Navy Environmental Health Center, May 1990),[25] to educate the Navy about PCB exposure, risk, and toxicity. This document was well researched and it includes a section on the structural and carcinogenic similarities between PCBs, PCDFs, and PCDDs shown below. It also states that PCDFs have been detected in relative high levels in some PCB batches.

Exhibit 25. *Excerpt from* Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzofurans (PCDFs), and Polychlorinated Dioxins (PCDDs): Structure of Biphenyl, Furan, and Dioxin

Dibenzo-furans and -dioxins are structurally similar to the biphenyls; having the same two phenyl rings, these molecules can be chlorinated to various degrees, just like the PCBs. The structural formulas of the unsubstituted dibenzo-furan and di-benzo-para-dioxin base compounds are given below:



Dibenzo-furans and -dioxins are found as trace contaminants in PCB products; they are derived as side products in the PCB manufacturing process. Studies have shown that the concentration of these contaminants can range from as low as 1 to as high as 500 ug/gm of PCB (Milby, 1985).

Source: Navy Environmental Health Center 1990.[25]

8. Because millions of different Aroclor mixtures and batches were produced by Monsanto and each batch of Aroclor contained varying amounts of PCDFs. It is more likely that the varying concentrations of the PCDF contaminants in the various Aroclor mixtures used in different cancer studies contributed to the differences in cancer rates and not the species of rat used by different laboratories in the 1970s and 1980s experiments.

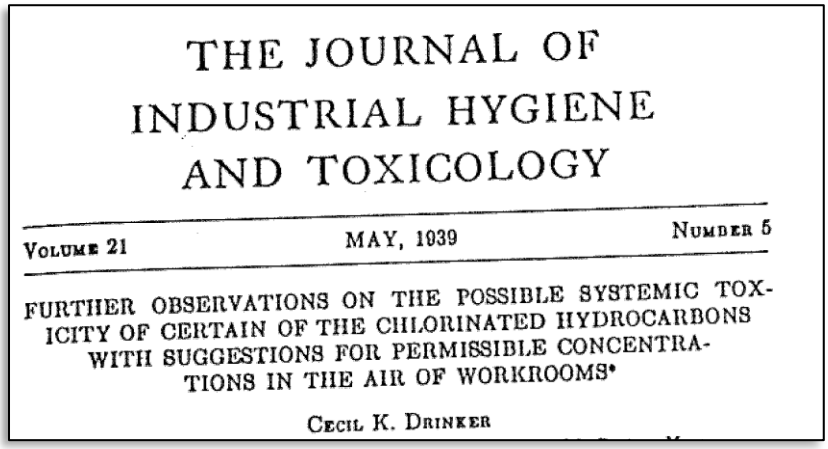
4. SPECIFIC RESPONSES TO DR. EATON'S CRITIQUES- PAGE 96

1. Dr. DeGrandchamp's comparative pathology analysis (beginning on Dr. DeGrandchamp Expert Report, April 5, 2019, p. 39) of Dr. Bennet's tested mixtures is methodologically flawed and scientifically.

My response:

Dr. Eaton misrepresents my opinion and the basis of that opinion. I was aware of the mix-up in the composition of the PCB test mixtures when I reviewed all of the Drinker studies. Dr. Eaton selectively extracted facts I stated in my opinion but failed to consider my entire testimony. My opinion was that adding a small amount (10%) of PCBs to the mixture of penta- and hexachloronaphthalene greatly increased the toxicity of that mixture compared to the mixture of penta- and hexachloronaphthalene without any PCBs. While Dr. Eaton correctly cited the Drinker studies, he omitted the most important part of that study that I discussed in my testimony. The study in question and the one I relied on was the following study:[26]

Exhibit 26. Cover Page from 1939 Drinker Study



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FURTHER OBSERVATIONS ON THE POSSIBLE SYSTEMIC TOXICITY OF CERTAIN OF THE CHLORINATED HYDROCARBONS WITH SUGGESTIONS FOR PERMISSIBLE CONCENTRATIONS IN THE AIR OF WORKROOMS*

CECIL K. DRINKER

Source: Drinker 1939.[26]

This is the study that describes the *apparent* mix-up in the chemical composition of the two complex mixtures. What is most important about this study is that it became the sole source of information about the safe exposure levels Dr. Drinker calculated based on his own study results in which he tested the safe exposure levels for 14 different mixtures considering both inhalation and ingestion routes of exposure. Ultimately these suggested permissible levels would become the sole point of reference that industry adopted for worker safety and information about the toxicity of the different mixtures. Dr. Drinkers table is shown below:

Exhibit 27. Table 1 from Drinker 1939: 14 Chlorinated Hydrocarbons, with Chlorine Contents and Permissible Limits for Air in Workrooms

TABLE 1

A List of 14 Chlorinated Hydrocarbons, with Chlorine Contents and Permissible Limits (in mg./cu.m.) for the Air in Workrooms*

Compound	Chlorine content	Permissible limit
	%	mg./cu.m.
1. Trichlornaphthalene plus a trace of tetrachlornaphthalene. Tested upon rats by inhalation and by feeding	49.9	10.0
2. Tetra and pentachlornaphthalenes. Tested upon rats by inhalation and by feeding	56.4	1.0
3. Penta and hexachlornaphthalenes. Tested upon rats by inhalation and by feeding, and upon dogs by feeding alone	62.6	0.5
4. Tetra and pentachlornaphthalenes plus refined chlorinated diphenyl. Tested upon rats by feeding	43.5	0.5
5. 90% penta and hexachlornaphthalenes plus 10% chlorinated diphenyl benzene. Tested upon rats by inhalation and by feeding	63.0	0.5
6. Chlorinated diphenyl plus chlorinated diphenyl benzene. Tested upon rats by inhalation and by feeding	65.0	0.5
7. Chlorinated diphenyl oxide. Tested upon rats by inhalation	54.0	0.5
8. Chlorinated diphenyl oxide. Tested upon rats by inhalation	57.0	0.5
9. Chlorinated diphenyl. Tested upon rats by inhalation	50-55	0.5
10. Hexachlor diphenyl oxide plus 5% trichlornaphthalene. Tested upon rats by inhalation	50-55	0.5
11. Hexachlornaphthalene and crude chlorinated diphenyl. Tested upon rats by inhalation	Unknown	0.5
12. Special chlorinated naphthalene. Tested upon rats by inhalation	50-56	0.5
13. Chlorinated diphenyl. Tested upon rats by inhalation	68	10.0
14. Chlorinated diphenyl benzene. Tested upon rats by inhalation	60	0.5

* The analytical method and apparatus used routinely for field determinations is that described by Tebbens (This J., *19*, 204 (1937)) and by Drinker *et al.* (ibid., p. 283).

Source: Drinker 1939.[26]

This table shows that for Mixture 2, which only contains tetra and pentachloronaphthalene the permissible level is 1.0 milligram/cubic meter. However, when refined PCB was added to that mixture (tetra and pentachlornaphthalene) the toxicity was *twice* as great as the Mixture of tetra and pentachlornaphthalene alone as the permissible exposure level was cut in half at: 0.5 milligram/cubic meter. Dr. Eaton failed to present or even discuss this table and these facts in his opinion.

Dr. Eaton's opinion that Mixture 2 *also* contained chlorinated diphenyl benzene is not supported by this *final* table of permissible levels that *all* PCB customers adopted as the "standard permissible" exposure levels of PCBs and chlorinated naphthalenes. If Dr. Eaton's opinion is correct then Dr. Drinker would have described Mixture 2 as containing tetra and pentachlornaphthalene and refined PCB *plus* chlorinated diphenyl benzene. The table does not state this fact. The table supports my opinion that Mixture 2 only contained the chlorinated naphthalene and PCBs.

It is conventional and generally accepted practices when scientists find an error in their published studies to issue an *erratum* to correct any errors. This is particularly true when the mistake could have grave consequences like publishing the permissible levels of exposure that are used as the sole metric to protect workers. I am not aware of any future publication that the Drinker team published any errata for any of the Drinker series of studies. They would also have issued an erratum for the earlier histopathological studies in which they state chlorinated diphenyl was the most toxic of all the compounds they tested:

> *Of the various chlorinated hydrocarbons tested, chlorinated diphenyl gave evidence of being the most toxic.*

This final definitive and clear conclusion that was stated in the Drinker study (Bennett et al. 1938) has never been retracted or modified or changed since this conclusion was reached.

Dr. Eaton also ignores the additional supporting facts from my testimony. I stated that my opinion that PCBs were extremely toxic and produced severe histopathologic lesions that were in fact identical to those reported by Dr. Miller of the Public Health Service (Miller, 1944) which were hyaline bodies. In fact, hyaline bodies were by far the most important morphological

damage he discussed. The most important fact from the Miller study was that there can be no dispute that PCBs *caused* these pathological lesions because animals were only exposed to PCBs were used in his study, a fact which Dr. Eaton failed to acknowledge or discuss. Indeed, he went on to stress that he was not only testing PCBs but that he was testing the "commercial" grade, which is the same formulation that Monsanto was selling to their customers (as opposed to a pure grade):

> *Only the pathologic changes in animals exposed to a commercial chlorinated diphenyl are given here.*

He stressed the fact that he is "only" reporting PCB-induced lesion because he was aware of the Drinker studies in which mixtures of PCBs and chlorinated naphthalenes were tested. His stated conclusion is consistent with mine as he references the same histopathological lesions that were reported in the Drinker studies. In comparing the Drinker study findings to his own, he came to the same conclusion I stated in my opinion. In fact, he stated the identical opinion about hyaline bodies lesions being greater in PCB-treated animals compared to chlorinated naphthalene. Based on his review of the Drinker studies and a comparison to his pathological findings of the hyaline lesions, he made the following conclusion:

> *The intracellular hyaline bodies were found in the rat liver alone…These findings agree with Bennett who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.*

Miller's statement is identical to mine, which I stated in my testimony.

2. Dr. DeGrandchamp misrepresents that mitotic bodies and hyaline bodies were markers for early hallmark of tumorigenesis at the time of the Drinker and Bennet studies in the 1930s.

My response:

Dr. Eaton misstates my opinion. I stated that mitotic figures and hyaline bodies *should have* been a trigger for Monsanto to conduct long-term cancer studies for PCBs. These two specific pathological lesions were established histopathological criteria identified and discussed in numerous historical studies I discussed in my report starting with the early 1900s. By the 1930s and 1940s they were key pathological criteria.

I did not state the appearance of mitotic figures and hyaline bodies were in fact *evidence that a tumor would develop* in the PCB-treated animals, because it would be impossible to make that prediction because the animals were killed at ~3 months. The final determination of the eventual outcome of those lesions is unknown and speculative. As I stated, the Drinker and Miller studies were subacute studies—not cancer studies. My opinion is that the appearance of those highly unusual pathological lesions that were described in the Drinker and Miller studies should have been a "trigger" or red flag as they were known to be lesions that were well-described in *other* (non-PCB) cancer studies. That is, I am posing the question of what would have been the eventual outcome of those highly damage rat livers if they were exposed to PCB in an actual chronic lifetime cancer study—should the uniqueness and severity of the lesions prompted an independent competent scientist to have concluded that it would be a good idea to start a long-term animal cancer study. Dr. Eaton holds a different opinion, seeming to conclude the pathology was seen in all types of liver damage. He therefore does not agree that the PCB lesions were important and that he would not have continued further toxicological investigations.

Dr. Eaton does not discuss the conclusions of Drinker and Miller with regard to both the severity and *uniqueness* of the hyaline bodies. Scientist typically choose the words they use to describe pathological features very carefully. Anytime a pathological description includes the term "peculiar" or unique it typically focuses the attention of other scientist reviewing their findings. This is how Drinker described the "peculiar" hyaline bodies:

> *Feeding of tetra- and pentachlornaphthalenes in combination with chlorinated diphenyl resulted in pronounced liver changes. These livers had increased in weight (average 71 per cent). Microscopic examination revealed a peculiar type of hyaline degeneration involving practically every liver cell (see figs. 1 and 2, plate I). This type of cell degeneration was more marked and occurred earlier after exposure to preparations containing chlorinated diphenyl than to any other compounds tested. Furthermore, it was most marked in the livers of animals exposed to refined chlorinated diphenyl (figs. 4, 5, and 6, plate III).*

Miller also focused on the presence of hyaline bodies in his PCB study far more than any other pathological feature and a photomicrograph of hyaline bodies was the *only one* he presented in his study.

Although, it is impossible to definitively conclude whether the PCB-induced lesions would have been repaired as Dr. Eaton's opinion suggests or whether the lesions would have developed into a carcinogenic response because the animals were killed too early. Neither of us can be certain- but I was not making a prediction. I was simply stating that since the lesions were "peculiar" or unusual and there were significant mitotic figures it was more likely that the liver would have proceeded to show true carcinogenic effects. Obviously, in retrospect my opinion is more likely since PCBs have been shown to precede along the same tumorigenic path when chronic animal testing was eventually carried out in the 1970s.

The one fact that Dr. Eaton ignores-or at least does not discuss in his report-which is the most important finding in the Drinker studies is that they stopped PCB dosing and the rats were allowed to recover from the liver damage; the livers did not recover and the damage was still the same. This evidence is contradictory to Dr. Eaton's opinion that the pathological lesions described by Drinker were simply the normal changes that occur during regeneration and repair from PCB-induced damage. Obviously, the damage was not due to repair processes. This apparently important enough to Drinker to run the study and report his findings.

> *In these instances the hyalin degeneration of the cell cytoplasm was more marked. Although rats inhaling low concentrations of compounds D and F showed no demonstrable signs of ill health, microscopic examination of their livers revealed marked liver cell injury (fig. 6, plate II, and fig. 3, plate III). These lesions were still demonstrable after a 2 months' recovery period.*

I also did not state that mitotic figures and hyaline bodies are *only* seen in cancerous tissue. I stated that it is possible that the histopathology could be due to regeneration-but as stated about was unlikely.

Finally, it is not clear if Dr. Eaton is suggesting that mitotic figures *are not* evidence of tumors. If this is the case, I disagree because tumor formation cannot occur without cell division. In fact, that is the very definition of a tumor-uncontrolled cell division. Mitotic figures are simply visual microscopic evidence of dividing cells. In the clinical setting, mitotic figures are perhaps the most important histological criteria that are used for tumor diagnoses, tumor staging, and tumor prognoses.

Lastly, I considered Dr. Millers finding that the hyaline bodies were not examples of pathologic changes. He specifically that hyaline bodies *were not seen* before *50 days* of exposure indicating they are more likely part of the carcinogenic sequelae rather than simple pathological lesions. If they were simple pathological lesions they would certainly be observed early in the pathological response-rather than only suddenly appearing after ~2 months of exposure which he states below:

> *Intracellular hyaline bodies were found in the liver of the rat alone. They were present, usually in large numbers, in all of the rats receiving 10 0.05-cc. doses and in some of the animals receiving 25 doses by skin and corneal applications and ingestion, but were not observed in any of the animals subjected to single doses. These bodies were noted in the animals sacrificed 50, 60, and 90 days after first exposure. None were observed in rats examined prior to 50 days on test. They occurred in from 20 to 38 percent of the animals treated in the various ways. They were somewhat less marked in degree and in number of animals when the chlorinated diphenyl was ingested. These findings agree with Bennett (7) who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.*

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